Environmental risk evaluation report: Perfluoroisohexane [PFiHx]

(CAS no. 355-04-4)

Chief Scientist's Group report

April 2023

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Dr Robert Bradburne
Chief Scientist

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Executive summary

There is growing regulatory concern at international level about the emissions of per- and polyfluoroalkyl substances (PFAS) to the environment. This is due to their extreme persistence, which could lead to long-term exposure of both people and wildlife. High levels of exposure to certain PFAS have also been shown to cause harmful effects in humans and some have been declared to be ‘Persistent Organic Pollutants’ (POPs) under the United Nations Environment Programme (UNEP) Stockholm Convention.

The UK Government is developing an action plan to address the concerns arising from PFAS. As a contribution to this work, the Environment Agency informally reviewed several PFAS that are made or used at two UK production facilities. The substance reviewed in this evaluation report is perfluoroisohexane or PFiHx (CAS no. 355-04-4).

PFiHx is a PFAS belonging to the group of perfluoroalkanes and is a liquid at standard environmental temperatures and pressures but is potentially volatile above approximately 50 °C. It is manufactured for use as a heat transfer fluid in the electronics industry and is also used in rigid foam blowing and as a tracer/taggant.

The Environment Agency has identified publicly available information on the regulatory status, uses, physico-chemical properties, environmental fate and (eco)toxicity of PFiHx and has reviewed this information for reliability and relevance. Further information has also been sought from the UK supplier. The data have then been used to conduct an environmental hazard and risk assessment as far as possible. Human health hazards have only been reviewed in so far as they are relevant for the environmental assessment. Potential risks to people following environmental exposure have not been addressed.

PFiHx is not readily biodegradable and there is no evidence that it degrades significantly via abiotic mechanisms. PFiHx therefore screens as Persistent (P) or very Persistent (vP). There are no valid aquatic bioconcentration data for PFiHx itself. In the absence of better information and based on Quantitative Structure-Activity Relationship (QSAR) approaches, a log K_{OW} of 4.5 is predicted, with an upper limit of 5. There is uncertainty whether perfluoroalkanes are within the applicability domain of the QSAR used, but this indicates that PFiHx meets the screening Bioaccumulative (B) criterion, and it cannot be ruled out that it screens as potentially very Bioaccumulative (vB). There are some indications of retention in mammalian tissues (which is possibly non-lipid mediated).

Regarding its toxicity (T), there is at present no conclusive information on PFiHx to determine whether it meets the criterion for ecotoxicity and read-across arguments from other perfluorocarbons are not well supported. The UK supplier does not identify any classification for PFiHx that would meet the human health ‘T’ criteria, although there are almost no mammalian toxicity data for the substance itself. The substance is not currently self-classified for aquatic hazard under Classification, Labelling and Packaging legislation,

but in the absence of reliable information, the Environment Agency recommends that the supplier self-classifies PFiHx as Aquatic Chronic 4.

Draft criteria have been proposed by the EU to identify chemicals that are persistent, mobile and toxic (PMT) or very persistent and very mobile (vPvM). PFiHx screens as P/vP and M but there is insufficient information to conclude whether it meets the T criterion. It might therefore pose a concern relating to the contamination of groundwaters.

Available information suggests it also has the potential for long-range transport. PFiHx is a structural analogue of perfluorohexane, which is a greenhouse gas identified in the Ozone-Depleting Substances (ODS) Substances and Fluorinated Greenhouse Gases (F-gas) regulations. It therefore likely presents the same risk to the environment once emitted to the atmosphere and is expected to have a significant global warming potential (GWP), with a 100-year GWP in the order of 8 000 to 9 300 $GtCO_2$-eq (see Section 9.5).

The direct emission estimates and Predicted Environmental Concentrations (PEC) for the manufacturing site in Section 10 of this report are based largely on default exposure modelling assumptions. Emissions from downstream uses within the UK have not been considered due to a lack of information. However, given the physico-chemical properties of PFiHx, a significant proportion of the overall production volume could eventually end up in the atmosphere (unless specific measures are taken to recover or destroy it). Certain potential downstream user industries (e.g. the semi-conductor industry) have exemptions from some F-gas controls.

In the absence of more detailed information regarding emissions, use pattern and measured environmental concentrations, there remains significant uncertainty in this assessment. Further refinement would be required to improve its reliability, which could include specific information on UK tonnages, uses and releases, monitoring data and more reliable experimental data for physico-chemical properties.

Given the uncertainty in the actual level of ecotoxicity posed by this substance, no relevant environmental Predicted No-Effect Concentration (PNEC) values have been calculated to perform a risk characterisation (Section 11) using the derived PEC values.

A number of recommendations are made to the UK supplier to improve the data package to allow a more robust assessment of the environmental hazards, exposure and risks posed by PFiHx, particularly relating to supporting and improving the scientific justification for the grouping and read-across data waivers in the physico-chemical properties, ecotoxicity and mammalian toxicity sections of their dossier. This report, along with others in this series, will be used by the Environment Agency to inform the UK Government action plan on PFAS and the PFAS Regulatory Management Options Analysis (RMOA) being conducted under the UK REACH Regulations.

Introduction

There is growing international concern about the emissions of per- and polyfluoroalkyl substances (PFAS) to the environment. This is principally due to their extreme persistence, which could lead to long-term irreversible exposure of both people and wildlife. High levels of exposure to certain PFAS has also been shown to cause harmful effects in humans and some have been declared to be ‘Persistent Organic Pollutants’ (POPs) under the United Nations Environment Programme (UNEP) Stockholm Convention.

The UK Government is developing an action plan to address the concerns arising from PFAS. As a contribution to this work, the Environment Agency informally reviewed several substances that are made or used at two known production facilities in the UK, namely AGC Chemicals Europe Ltd of Thornton Cleveleys, Lancashire and F2 Chemicals Ltd of Preston, Lancashire. Based on information provided by these companies, a provisional list of PFAS for further consideration was drawn up. This was narrowed down to the following eight substances which were, at the time, registered at more than 1 tonne per year under the EU REACH Regulation[1] and subsequently also under UK REACH. Additionally a potential substitute for perfluoroctanesulfonic acid (PFOS, which is a known POP) was included that had been identified from UK surface water monitoring. All of the substances chosen for further evaluation are listed below, initially using their EU-registered name:

- Ammonium difluoro[1,1,2,2-tetrafluoro-2-(pentafluoroethoxy)ethoxy]acetate - also known as perfluoro(2-ethoxy-2-fluoroethoxy)acetic acid ammonium salt or EEA-NH_4 (CAS no. 908020-52-0)
- Trideca-1,1,1,2,2,3,3,4,4,5,5,6,6-fluorohexane - also known as 1H-perfluorohexane or 1H-PFHx (CAS no. 355-37-3)
- 3,3,4,4,5,5,6,6,6-Nonafluorohexene - also known as perfluorobutylethylene or PFBE (CAS no. 19430-93-4)
- 1,1,1,2,2,3,3-Heptafluoro-3-[(trifluorovinyl)oxy]propane - also known as perfluoro(propyl vinyl ether) or PPVE (CAS no. 1623-05-8)
- **1,1,1,2,2,3,3,4,5,5,5-Undecafluoro-4-(trifluoromethyl)pentane - also known as perfluoroisohexane or PFiHx (CAS no. 355-04-4)**
- Perflunafene - also known as perfluorodecalin or PFD (CAS no. 306-94-5)
- Hexafluoropropene or HFP (CAS no. 116-15-4)

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[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) - see: https://ec.europa.eu/environment/chemicals/reach/reach_en.htm

- Octafluoropropane - also known as perfluoropropane or PFP (CAS no. 76-19-7)

The additional substance also being considered is:

- 6:2 Chlorinated polyfluorinated ether sulfonate, 6:2 Cl-PFESA - also known as ‘F-53B’ (CAS no. 73606-19-6)

This report summarises the evaluation of the substance highlighted above in **bold** (i.e. PFiHx), to address the following questions:

- What data are currently available, and are they sufficiently reliable to assess the environmental hazards and risks from this substance?
- Can we establish numerical exposure limits for assessing environmental impacts (e.g. for use under permitting regimes)?
- Is this substance potentially able to reach remote environments and what is its groundwater contamination potential?
- Is this substance a potential candidate for future risk management?
- What information gaps remain, relative to the registered tonnage of this substance and, if required, what is the most appropriate way of obtaining this information?

The Environment Agency has performed a literature review on this substance (Appendix A: Literature search). As the substance was, at the time of writing, registered under EU REACH, information on the properties and uses of the substance was obtained from the European Chemicals Agency (ECHA) public dissemination website (ECHA, 2020; ECHA, 2020a). Unless otherwise stated, this website is the main source of information used in this report. Full scientific study reports have generally not been reviewed by the Environment Agency, only the publicly available literature and EU REACH dossier information have been consulted at this stage. Some additional information was also provided by the UK supplier.

This report describes the substance and its structural analogues, its analytical chemistry, manufacture and use, regulatory status and then various environmentally relevant properties. This is followed by an environmental hazard assessment in Section 9, then an exposure and risk assessment. The final section summarises the findings of this review. Although the focus of this evaluation is on environmental hazards and risks, there is a brief summary of mammalian toxicology information where available and relevant to the environmental assessment. This report is however not intended to provide a consideration of hazards, exposure and risks to human health. This is <u>not</u> a formal UK REACH Evaluation.

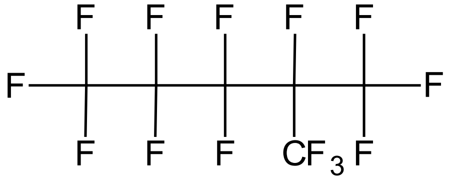
1 Substance identity

1.1 Name and other identifiers

Public name	Perfluoro-2-methylpentane
IUPAC name	Perfluoro-2-methylpentane
CAS name	-
Alternative name	Perfluoroisohexane or PFiHx*
EC number	206-575-6
CAS number	355-04-4
Index number in Annex VI of the CLP Regulation	-
Molecular formula	C_6F_{14}
Molecular weight	338 g/mol
SMILES code	C(C(C(C(F)(F)F)(F)F)(F)F)(C(F)(F)F)(C(F)(F)F)F
Synonyms	Perfluoro(2-methylpentane), tetradecafluoro-2-methylpentane
Type of substance	Mono-constituent

Note: * The substance is referred to using its abbreviated form [PFiHx] for the purposes of this report.
SMILES - Simplified Molecular Input Line Entry System

Figure 1.1 Structural formula of PFiHx



1.2 Structurally related substances

PFiHx is a branched perfluoroalkane, with a perfluoromethyl group in the 2-position. It is an example of a perfluorocarbon (PFC), containing only carbon and fluorine atoms. Substances in the perfluoroalkane category have fully fluorinated (i.e. saturated) carbon atoms and lack functional groups such as the acids, ethers or alcohols that characterize other PFAS categories (OECD, 2018).

The US EPA CompTox Chemicals database (US EPA, 2020a; US EPA, 2020b) was used to identify key structural analogue(s) of PFiHx. The carbon-fluorine bond is very strong (up to 546 kJ/mol in tetrafluoromethane (CF_4)) and so PFCs are much less reactive than their hydrocarbon analogues.

A structural isomer is perfluorohexane (it has a straight carbon chain, unlike PFiHx), as described in the substance identifier list below.

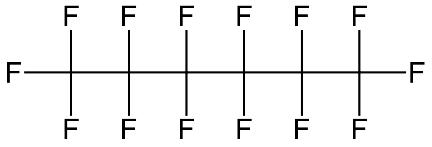
Public name: Perfluorohexane

IUPAC name: 1,1,1,2,2,3,3,4,4,5,5,6,6,6-tetradecafluorohexane

CAS number: 355-42-0

EC number: 206-585-0

Figure 1.2 Structural formula of perfluorohexane:



Molecular formula: C_6F_{14}

Molecular weight: 338 g/mol

SMILES code: C(C(C(C(F)(F)F)(F)F)(F)F)(C(C(F)(F)F)(F)F)(F)F

Synonyms: Perflexane, perfluoro-n-hexane, tetradecafluorohexane

Relationship to PFiHx: Belongs to the perfluoroalkane group and is a structural isomer of PFiHx

Non-fluorinated hydrocarbons have been considered briefly in Section 5, to illustrate how branching of different isomers might affect some properties.

1.3 Transformation products

Information from Section 6 of this report indicates that PFiHx is very stable and unlikely to react or degrade further through biotic or abiotic means. Consideration of further transformation products is therefore not relevant for the purposes of this report.

2 Analytical chemistry

2.1 Regulatory and academic methods

No analytical details are included in the EU REACH registration dossier (ECHA, 2020a).

The Environment Agency searched the academic literature for analytical methods for the detection of PFiHx in the following environmental matrices: water, fresh and marine; soil; sediment; sludge; and air (see Appendix A: Literature search). No environmental monitoring methods for PFiHx were identified.

Analytical monitoring of PFiHx environmental matrices does not appear to be performed as part of national or international programmes. In particular, it is not present in the following PFAS databases accessed via the NORMAN network (https://www.norman-network.com/nds/susdat/ accessed 12 February 2021):

- PFASTRIER list - although the structural analogue perfluorohexane is listed; and
- PFASNTREV19.

PFiHx was included in a KEMI PFAS List (KEMI, 2015) and PFAS list published by the Organisation for Economic Co-operation and Development (OECD, 2018) but no associated analytical methods were presented.

Internationally validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) methods for the analyses of specific PFAS in general include several methods used by the United States Environmental Protection Agency (US EPA), of which none were found to include PFiHx.

It is recommended that the UK supplier provides details of their analytical methodology for measuring atmospheric emissions of PFiHx (and related PFCs). The Environment Agency considers that the description of a robust analytical method will typically include the following details:

- Instruments and consumables including chromatographic column, temperature, mobile phase composition, flow rates, gradient or isocratic separation and the detector optimisation and configuration.
- Certified reference standards, calibration range and sensitivity, limit of detection, limit of quantification, column recoveries, stability and reproducibility.
- The use of procedural blanks and control samples in both sample preparation and analysis.
- Sample preparation including clean-up consumables, concentration techniques and use of internal standards (plus justification for choice) for validation and recoveries, etc.

- Identification and discussion of technical limitations.

3 Import, manufacture and uses

Although the UK left the European Union (EU) at the end of January 2020, European legislation in place by December 2020 has been retained and transposed in to UK law, and the European Chemicals Agency (ECHA) public databases are, at the time of writing, still a relevant source of information about industrial chemicals on the UK market.

According to the ECHA website (ECHA, 2020a), PFiHx is registered in the EU by Chementors Ltd, Raisio, Finland (a consultancy firm) at an aggregated supply level of 100 to 1 000 tonnes/year (ECHA, 2020a). The substance is manufactured by F2 Chemicals Ltd (www.f2chemicals.com), Preston, Lancashire. Personal communication with F2 Chemicals Ltd shows that their manufacture and supply is within this registration tonnage band.

F2 Chemicals Ltd has an environmental permit (ref: EPR/BU3485IS) under the Environmental Permitting (England and Wales) Regulations 2016. It produces a range of liquid and gaseous PFC substances, with a total production capacity of around 400 tonnes/year.

An overview of uses according to the public EU REACH registration is presented in Table 3.1. The F2 Chemicals Ltd website provides some additional details (http://www.f2chemicals.com/perfluoro-2-methylpentane.html accessed August 2020). PFiHx's characteristics are said to include:

- compatibility with most construction materials;
- excellent chemical and thermal stability;
- non-flammability; and
- limited toxicity.

Applications include use as a fluid in the electronics industries for testing and direct contact/ submersion cooling, as a heat transfer fluid in organic Rankine engines (which perform heat recovery from low temperature sources such as biomass combustion, industrial waste heat, geothermal heat, solar ponds, etc.; the low-temperature heat can be converted into electricity) as well as in rigid foam blowing and as a tracer and taggant (e.g. for use in the oil industry).

Table 3.1 Overview of uses

Life cycle stage	Use(s)
Manufacture	**Manufacture of substance** ERC1: Manufacturing PROC 4: Chemical production where opportunity for exposure arises
Formulation	None identified in the registration dossier
Uses at industrial sites	None identified in the registration dossier
Uses by professional workers	None identified in the registration dossier
Consumer uses	None identified in the registration dossier
Article service life	None identified in the registration dossier

Source: EU REACH registration dossier (ECHA, 2020a)

4 Summary of relevant regulatory activities

4.1 Europe

4.1.1 European Chemicals Agency (ECHA)

The Public Activities Co-ordination Tool (PACT) (https://echa.europa.eu/pact accessed July 2020) provides an overview of the substance-specific activities that EU regulatory authorities are working on under the EU REACH and CLP Regulations. PFiHx is not currently included on PACT, and neither is it listed on the Community Rolling Action Plan (CoRAP) (https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table accessed July 2020).

Between May and July 2020, the national authorities of Germany, the Netherlands, Norway, Sweden and Denmark invited interested parties to send in evidence and information on the use of PFAS in preparation for a joint EU REACH restriction proposal (see: https://www.rivm.nl/en/pfas/pfas-restriction-proposal accessed July 2020). The current scope of the work is wide and includes all substances that contain at least one aliphatic -CF_2- or -CF_3 element, PFiHx is therefore within scope of this initiative (see ECHA Registry of Restriction Intentions: https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18663449b, accessed October 2021).

4.1.2 European Food Safety Agency (EFSA)

EFSA provides scientific advice on safety of food additives, enzymes, flavourings, processing aids and other substances intentionally added to food; safety of food packing and other food contact materials.

A search of EFSA (http://www.efsa.europa.eu/ accessed July 2020) did not identify PFiHx as being evaluated in any published scientific opinions.

4.1.3 Oslo and Paris Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR)

The Oslo and Paris Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR) is a mechanism by which 15 national governments and the EU co-operate to protect marine resources. Much of OSPAR’s work on chemicals is now being addressed by EU REACH activities.

PFiHx is not on the OSPAR List of Substances of Possible Concern (https://www.ospar.org/work-areas/hasec/hazardous-substances/possible-concern accessed July 2020), nor on the list of Chemicals for Priority Action adopted in 2002 (https://www.ospar.org/work-areas/hasec/hazardous-substances/priority-action accessed July 2020).

4.2 Regulatory activity outside of Europe

4.2.1 United States of America

The US EPA is planning to carry out tiered toxicity and toxicokinetic testing for a range of PFAS in the near future (Patlewicz *et al.,* 2019). PFiHx is not listed in the Patlewicz *et al.* study. The US EPA have a PFAS Strategic Roadmap which sets out their commitments to action for the period 2021-2024 (https://www.epa.gov/pfas/pfas-strategic-roadmap-epas-commitments-action-2021-2024 accessed October 2021).

PFiHx is not listed as one of the substances undergoing risk evaluation as part of the US EPA's existing chemical initiative under the Toxic Substances Control Act (TSCA) to determine whether they present an unreasonable risk to public health or the environment under the conditions of use (https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/chemicals-undergoing-risk-evaluation-under-tsca accessed July 2020; https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/low-priority-substances-under-tsca accessed July 2020).

4.2.2 Canada

A search did not identify PFiHx as being under assessment under the Prohibition of Certain Toxic Substances Regulations, 2012 (https://www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/substances-list/toxic.html accessed July 2020).

4.2.3 Australia

A search did not identify PFiHx as being under assessment under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (https://www.industrialchemicals.gov.au/chemical-information/search-assessments accessed July 2020).

4.2.4 New Zealand

A search did not identify PFiHx as being under assessment under the Hazardous Substances and New Organisms Act 1996 (https://www.epa.govt.nz/industry-areas/hazardous-substances/chemical-reassessment-programme/screened-chemicals-list/ accessed July 2020).

4.2.5 Japan

Industrial chemicals are managed under the Chemical Substances Control Law (CSCL), most recently amended in 2009 (https://www.nite.go.jp/chem/jcheck/list3.action?Category=141&request_locale=en accessed July 2020) Under the Act there are 3 lists:

- Class I Specified Chemicals - 28 substances (persistent, bioaccumulative, toxic)
- Class II Specified Chemicals - 23 substances (toxic and high risk)
- Priority Assessment Chemical Substance (PACS), currently 226 substances

PFiHx is not on any of the above lists.

4.3 Other international agreements

4.3.1 United Nations Stockholm Convention on Persistent Organic Pollutants (POPs)

PFiHx is not identified as a POP, and is not currently under evaluation (http://chm.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx accessed July 2020).

4.3.2 Greenhouse gases

Fluorinated gases (‘F-gases’) may contribute to climate change due to their global warming potential and they are often used as substitutes for ozone-depleting substances, because they do not damage the atmospheric ozone layer (EC, 2015). F-gases are regulated under the Ozone-Depleting Substances and Fluorinated Greenhouse Gases (Amendment etc.) (EU Exit) Regulations (2019) (https://www.legislation.gov.uk/uksi/2019/583/contents/made accessed 12 February 2021) which aims to reduce the emission of these gases into the environment. PFiHx is not included in the listed F-gases subject to the Regulation, but its chemical isomer/analogue perfluorohexane is (see Section 9.5).

5 Physico-chemical properties

This evaluation focusses on vapour pressure, water solubility and n-octanol-water partition coefficient, because they are the key physico-chemical endpoints for the environmental assessment of most organic chemicals. Surface tension and dissociation constant are also considered. The available information is discussed in this section, and a conclusion drawn about which value the Environment Agency considers most suitable for the further evaluation of this substance.

The source of this information is the publicly available EU REACH registration database (ECHA, 2020a; accessed July 2020) unless otherwise indicated. The reliability scores provided in the full registration for individual studies are cited. These scores have presumably been generated in accordance with the ECHA R.4. Guidance Document (ECHA, 2011). An independent evaluation has not been possible since original study reports were not available, and the EU REACH registration dossiers generally lack sufficient supporting information. The Environment Agency is therefore not in a position to assign its own reliability scores (except in the case of data presented in academic journals or obtained using quantitative structure-activity relationship (QSAR) models). Nevertheless a general interim view of study reliability is made.

Where an endpoint value is missing from the EU REACH registration dossier, or an initial review raised questions around the validity of an experimentally derived value, the assessment has been supplemented with information from analogues (see Section 1) and openly available *in silico* QSAR models. EU REACH registration data for the analogues are taken at face value, although preference is given to regulatory reviews (if available). QSAR models are generally considered to be a screening-level tool and measured values are preferable provided that they are sufficiently reliable. Further information on QSARs is provided in Appendix B: QSAR models.

An overview of physico-chemical data provided in the EU REACH registration or generated by the Environment Agency is presented in Table 5.1 Summary of physico-chemical properties:

Table 5.1 Summary of physico-chemical properties

Property	Value(s)	Reliability	Reference
Physical state at 20°C and 101.3 kPa	Clear colourless liquid	Registrant: 2 (key study)	Registration dossier
Melting / freezing point	-90 °C (method unknown, unnamed study)	Registrant: 2 (key study)	Registration dossier
Boiling point	57 °C (calculated from vapour pressure, unnamed study)	Registrant: 2 (key study)	Registration dossier
Relative density	1.73 g/m^3 at 20 °C (pycnometer method) (Stiles and Cady, 1952)	Registrant: 2 (key study)	Registration dossier
Vapour pressure	29 kPa at 25 °C (measured using isoteniscope) (Stiles and Cady, 1952; Crowder *et al.*, 1967)	Registrant: 2 (key study)	Registration dossier
Surface tension	11.91 mN/m (capillary rise method) (Stiles and Cady, 1952)	Registrant: 2 (key study)	Registration dossier
Water solubility	<0.1mg/L	Registrant: 2 (key study)	Registration dossier
n-Octanol/water partition coefficient (log K_{OW})	>3.74 at 21.5 °C (shake flask method, OECD TG 107, GLP compliant)	Registrant: 1 (key study)	Registration dossier
Particle size distribution	Not relevant. The substance is a liquid at room temperature and atmospheric pressure.	-	Registration dossier
Stability in organic solvents and identity of relevant degradation products	Stable in all solvents.	Registrant: 2 (key study)	Registration dossier
Dissociation constant	Data waiver 'does not dissociate'.	-	Registration dossier

5.1 Vapour pressure

5.1.1 Measured data

An experimentally derived vapour pressure value of 29 kPa at 25 °C (isoteniscope method) was presented in the EU REACH registration dossier of PFiHx (ECHA, 2020a).

This key study is referenced to Stiles and Cady (1952) and Crowder *et al.* (1967) and was classed as not GLP compliant. The EU REACH registration assessed the data reliability as Klimisch score 2 (reliable with restrictions). No details of methodology were provided.

The ChemSpider database contained a measured vapour pressure for PFiHx of 23.5 kPa at 20 °C (176 mmHg at 20 °C; value converted from mmHg to kPa by the Environment Agency) (RSC, 2020a). No details of methodology were provided.

5.1.2 Predicted data

No *in silico* predictive data were presented in the EU REACH registration for this endpoint.

The ChemSpider database and the US EPA CompTox dashboard contain predicted vapour pressures for PFiHx generated from EPISuite^{TM}, T.E.S.T., ACD/Labs and OPERA software (RSC, 2020a) (US EPA, 2020a). Median predicted values are presented in Table 5.2 Predicted vapour pressures for PFiHx. The Environment Agency converted the values from mmHg to kPa.

Table 5.2 Predicted vapour pressures for PFiHx

Source	Details	Vapour pressure at 25 °C
ACD/Labs	-	28.3 kPa [212 mmHg]
EPISuite™ estimation programme MPBPVP v1.42	Mean of Antoine and Grain methods BP = 49.54°C MP = -88.87°C	29.7 kPa [223 mmHg]
T.E.S.T.	-	57.7 kPa [433 mmHg]
OPERA	Global applicability domain: Inside Local applicability domain index: 0.591 Confidence interval 0.402	54.3 kPa [407 mmHg]

In silico predicted values should always be treated with caution where substances in the training set and external test set are not visible.

- For the ACD/labs model this information was not available. Therefore no assessment of the applicability could be performed.
- Guidance provided with the MPBPWIN v1.42 model indicated that the relationship between the experimental and predicted vapour pressure values for a test set of 1 642 compounds was good, with an R^2 of 0.949, standard deviation of 0.59 and an average deviation of 0.32. The training set contained several PFCs (see Appendix B: QSAR models) including perfluorohexane and it is likely that the predicted value for PFiHx falls within the applicability domain of the model.

- For the OPERA model, PFCs were included in both the training set and external test sets (e.g. perfluoropentane and perfluorobutane). PFiHx is considered inside the global applicability domain and has a high local applicability domain index (~0.6), so the prediction is considered reliable based on the OPERA model applicability domain criteria.
- For the T.E.S.T. model, PFCs were included in both the training set and external test sets (e.g. perfluoroheptane). Therefore, predicted values from T.E.S.T. could be considered within the applicability domain of the model.

5.1.3 Data from structural analogues

The Environment Agency has sought data for perfluorohexane. In comparison with this substance, PFiHx has the same molecular weight and is a similar structure. It is therefore likely to be of similar volatility.

A predicted vapour pressure value of 26.5 kPa at 25 °C was presented in the EU REACH registration dossier of perfluorohexane (ECHA, 2020b). The EU REACH registration assessed the data reliability as Klimisch score 2 (reliable with restrictions).

The ChemSpider database and US EPA CompTox dashboard (RSC, 2020b; US EPA, 2020b) both contained a measured vapour pressure value for perfluorohexane of 29.1 kPa at 25 °C (218 mmHg at 25 °C; value converted from mmHg to kPa by the Environment Agency). No details of methodology or reliability were provided.

Given the lack of background information about this measured value, the Environment Agency checked the ChemSpider database and the US EPA CompTox dashboard contains predicted vapour pressures for perfluorohexane generated from EPISuite^{TM}, T.E.S.T., ACD/Labs and OPERA software (RSC, 2020b). (US EPA, 2020b). Median predicted values are presented in Table 5.3 Predicted vapour pressures for perfluorohexane. The Environment Agency converted the values from mmHg to kPa.

Table 5.3 Predicted vapour pressures for perfluorohexane

Source	Details	Vapour pressure at 25 °C
ACD/Labs	N/A	30.4 kPa [227.9 mmHg]
EPISuite™ estimation programme MPBPVP v1.42	Mean of Antoine and Grain methods BP = 49.54°C MP = -88.87°C	31.9 kPa [239 mmHg]
T.E.S.T.	N/A	18.4 kPa [138 mmHg]
OPERA	Global applicability domain: Inside Local applicability domain index: 0.997 Confidence interval 0.71	29.3 kPa [220 mmHg]

The Environment Agency notes with the exception of the T.E.S.T. model, these predicted values are all around 30 kPa, which is very similar to the reported measured value.

5.1.4 Additional sources

No additional relevant information was reviewed as part of this evaluation.

5.1.5 Recommended value

For PFiHx a vapour pressure value of 29 kPa (at 25 °C) was measured (ECHA, 2020a). *In silico* predicted values range from 28.3 kPa to 57.7 kPa (all at 25 °C; US EPA, 2020a and RSC, 2020a).

The Environment Agency is not able to assess the validity of the experimentally derived value presented in the EU REACH registration, due to the age of the studies and the lack of detail in the supporting information to review the methodology against current test guidelines (e.g. OECD Test Guideline (TG) 104; OECD, 2006). The Environment Agency recommends that the robust study summary for this endpoint is updated. However, this value is within the range of *in silico* derived values from a range of models (and is very close to 2 of them) and is very similar to the value reported for the close structural analogue perfluorohexane.

The Environment Agency therefore considers that a vapour pressure of **29 kPa at 25°C** is suitable for use in the exposure and risk assessment.

5.2 Surface tension

5.2.1 Measured data

An experimentally determined surface tension of approximately 11.91 mN/m at 25 °C is included in the EU REACH registration of PFiHx, referenced as Stiles *et al.* (1952) (ECHA, 2020a). The value was not considered GLP compliant and was measured using the capillary rise method. No further information was presented. The EU REACH registration gave the study a Klimisch score of 2 (reliable with restrictions). No detailed study methodology or analytical details were reported in the original reference.

The Environment Agency considers that this is the surface tension of the substance itself rather than that of an aqueous solution and so is not relevant for this evaluation (see Section 5.2.4).

The EU REACH registration provided surface tension measured data on PFiHx in response to requests for further information made by the Environment Agency. An experimentally determined surface tension of approximately 72 mN/m at 25 °C was reported for PFiHx in water (Unpublished, 2021a). A liquid sample of PFiHx was measured using a Data Physics DCAT 21 tensionmeter and the Wilhelmy plate method. The liquid was measured 3 times and the test plate was cleaned before each measurement. No indication of GLP or reliability of the study was provided.

5.2.2 Predicted data

The ChemSpider database (RSC, 2020a) and US EPA CompTox dashboard (US EPA, 2020a) include predictions of surface tension that are of a similar order of magnitude as the reported measured value.

5.2.3 Data from structural analogues

No information from the structural analogue was considered necessary.

5.2.4 Additional sources

Chernyshev and Skliar (2014) reported a substantial decrease in the surface tension of deionised water in the presence of PFC vapours in an experiment using perfluoropentane and perfluorohexane at 20 °C. The surface tension of the water reduced from 72 mN/M to 64.6 mN/M in the presence of perfluoropentane and 66.7 mN/M in the presence of perfluorohexane.

As part of this evaluation, the Environment Agency reviewed data for perfluorophenanthrene (CAS no. 306-91-2). It is reported to have a minimal effect on the surface tension of water. Whilst not a close analogue of HFP, the lack of hydrophilic functional groups means that PFCs generally are unlikely to be surface active in water.

5.2.5 Recommended value

Surface tension in water is important because it affects the measurement and interpretation of other physico-chemical properties such as water solubility and partition coefficients. There is no legal requirement to provide a surface tension value for substances with a water solubility below 1 mg/L. It is likely that this applies to PFiHx (see Section 5.3).

Although the EU REACH registration reports a measured surface tension of 11.91 mN/m at 25 °C for PFiHx, the Environment Agency considers that this is the surface tension of the neat substance rather than that of an aqueous solution and so is not relevant for this evaluation (based on information from Chernyshev and Skliar, 2014). Further information provided in the EU REACH registration is that the surface tension of the water was not reduced from 72 mN/M by the presence of PFiHx.

The Environment Agency notes that PFiHx does not have any hydrophilic structural groups that can form hydrogen or van der Waals bonds in water. This suggests that it is unlikely to be significantly surface active in aqueous solutions. Evidence from Chernyshev and Skliar (2014) for perfluorohexane suggests that there is some potential for the formation of a separate PFiHx layer at the water-air interface in aqueous solution. The Environment Agency recommends that the robust study summary for this endpoint is updated.

5.3 Water solubility

5.3.1 Measured data

No experimentally derived water solubility value was presented in the EU REACH registration dossier of PFiHx. The substance is said to be ‘insoluble’ with a water solubility of 0.01 mg/L at 20 °C sourced from “other company data, data from various sources, including read-across from similar PFCs” (ECHA, 2020a).

The EU REACH registration provided water solubility data on PFiHx in response to requests for further information made by the Environment Agency. The solubility of PFiHx was reported at <0.1 mg/L at 20 °C. No indication of GLP or reliability of the study was provided. (Unpublished, 2021b).

5.3.2 Predicted data

No *in silico* predictive data were presented in the EU REACH registration for this endpoint.

The ChemSpider database and US EPA CompTox dashboard contained predicted water solubility endpoint values generated from EPISuite™, T.E.S.T. and OPERA software (RSC, 2020a; US EPA, 2020a). These values are presented in Table 5.4. Values were converted by the Environment Agency from mol/L to mg/L using a molecular weight of 338.04 g/mol.

Table 5.4 Predicted water solubility values for PFiHx

Model	Details	Water Solubility
EPISuite™ water solubility estimate from log K_{OW} (WSKOW v1.41)	Log K_{OW} used: 5.31 (estimated) no-melting point equation used	0.038 mg/L at 25 °C
EPISuite™ water solubility estimate from fragments (v1.01 est.)	-	0.0054 mg/L
T.E.S.T.	Predicted value: 1.67×10^{-5} mol/L	5.64 mg/L
OPERA	Predicted value: 3.47×10^{-5} mol/L Global applicability domain: Outside Local Applicability domain index: 0.308 Confidence Interval 0.483	11.72 mg/L

In silico predicted values should always be treated with caution where substances in the training set and external test set are not visible.

- Guidance provided with the WSKOWWIN v1.41 model indicates that the relationship between the experimental and predicted values for a training set of 1 450 compounds was good, with an R^2 of 0.97, standard deviation of 0.409 and an average deviation of 0.313. The validation set contained several PFCs (see Appendix B: QSAR models) including structurally similar substances of PFiHx (e.g. perfluoropropane) and it is likely that the predicted value for PFiHx falls within the applicability domain of the model but the value should still be treated with caution.
- For the T.E.S.T. model, no close PFCs were included in both the training set and external test sets. Therefore, predicted values from T.E.S.T. could be considered to be outside the applicability domain of the model.
- For the OPERA model, PFCs were included in both the training set and external test sets (e.g. perfluoropropane). PFiHx is considered outside the global applicability domain and has a low local applicability domain index (< 0.4), so the prediction is not considered reliable based on the OPERA model applicability domain criteria.

5.3.3 Data from structural analogues

The Environment Agency has sought data for perfluorohexane as no numerical data were available in the EU REACH registration dossier for PFiHx. PFiHx and perfluorohexane are isomers, so there is likely to be only a minor difference in water solubility[2].

A water solubility of < 0.1 mg/L at 25 °C using the column elution method according to OECD TG 105 (OECD, 1995a) is cited in the EU REACH registration of perfluorohexane (ECHA, 2020b). The source was an unnamed study report (2018); the method was GLP compliant. The EU REACH registration gave the study a Klimisch score of 1 (reliable without restrictions).

For comparison, the ChemSpider database contained estimated water solubilities from EPISuite™ (RSC, 2020b). The US EPA CompTox dashboard contained predicted water solubility endpoint values generated from EPISuite™, T.E.S.T. and OPERA software (US EPA, 2020b). Values are presented in Table 5.5 Predicted water solubility values for

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[2] For example, in the case of non-fluorinated hydrocarbons, data from ECHA's public dissemination website indicates that n-hexane and 2-methylpentane have a water solubility of 9.8 and 14 mg/L at 25 °C, respectively.

perfluorohexane. Values were converted by the Environment Agency from mol/L to mg/L using a molecular weight of 338.04 g/mol.

Table 5.5 Predicted water solubility values for perfluorohexane

Model	Details	Water Solubility
EPISuite™ water solubility estimate from log K_{OW} (WSKOW v1.41)	Log K_{OW} used: 6.02 (estimated) no melting point equation used	0.0095 mg/L at 25 °C
EPISuite™ water solubility estimate from fragments (v1.01 est.)	-	0.0018 mg/L
T.E.S.T.	Predicted value: 2.26×10^{-5} mol/L	7.64 mg/L
OPERA	Predicted value: 3.34×10^{-5} mol/L Global applicability domain: Inside Local Applicability domain index: 0.315 Confidence Interval 0.486	11.29 mg/L

This suggests that the EPISuite™ models are more relevant than the other two for this endpoint and substance type.

5.3.4 Additional sources

Tsai *et al.* (2002) and Tsai (2009) roughly estimated the water solubility of several PFCs from the measured water solubility of tetrafluoromethane. The estimation was performed using a regression equation derived from plotting water solubility against octanol-water partition co-efficient. These values are summarised in Table 5.6 Summary of estimated water solubility of PFC analogues.

Table 5.6 Summary of estimated water solubility of PFC analogues

Substance	Molecular weight (g/mol)	Water solubility (mol/L)	Water solubility (mg/L)	Measured/ estimated	Reference
Perfluoromethane	88	1.7×10^{-4}	15.0	Not stated	Tsai *et al.*, (2002)
Perfluoromethane	88	2.1×10^{-4}	18.5	Measured†	Tsai (2009)
Perfluoropentane	288	1.9×10^{-5}	5.5	Estimated	
Perfluorohexane	**338**	$\mathbf{1.0 \times 10^{-5}}$	**3.4**	**Estimated**	
Perfluoroheptane	388	5.7×10^{-6}	2.2	Estimated	
Perfluorooctane	438	3.1×10^{-6}	1.4	Estimated	
Perfluorononane	488	1.7×10^{-6}	0.8	Estimated	

†measured at 25 °C

The Environment Agency does not consider this to be a reliable approach, given the uncertainties in the octanol-water partition coefficients used in this study (see Section 5.4) and the fact that some of the substances are gases. This approach over-estimates the water solubility of perfluorohexane compared to the EU REACH information.

5.3.5 Recommended value

The key water solubility value of 0.01 mg/L at 20 °C presented in the EU REACH registration lacks description and documentation of the read across approach used (including source data reliability). The Environment Agency recommends that the robust study summary is updated using ECHA's Read-Across Assessment Framework (RAAF) (ECHA, 2017a) to provide greater clarity. Further information was provided in the EU REACH registration to indicate that the water solubility value of PFiHx is <0.1 mg/L at 20 °C.

The Environment Agency notes that according to Chernyshev and Skliar (2014), PFCs such as perfluorohexane form colloids in water, which may involve "liquid droplets, vapour bubbles or a combination of both phases simultaneously". PFiHx is likely to partition from water to air (see Section 6.2.2), so controls to limit losses due to volatility may also be required during measurement. Both factors complicate the measurement of aqueous solubility.

In silico predictions for the water solubility of PFiHx were between 0.0054 and 11.7 mg/L (RSC, 2020a; US EPA, 2020a). Although this is a very wide range, the lower estimates appear to be more realistic based on evidence from the analogue perfluorohexane (which has a reported measured water solubility in the EU REACH registration of < 0.1 mg/L at 25 °C). Given the issues around colloid formation and volatility for this type of substance, the perfluorohexane result may not be fully reliable. The studies of Tsai *et al.* (2002) and Tsai (2009) suggest a water solubility of 3.4 mg/L for perfluorohexane, but the Environment Agency considers this to be unreliable.

In the aquatic toxicity studies, exposure solutions appear to have been prepared up to a nominal concentration of 0.1 mg/L with the aid of a dispersant, although further details are not available (including test substance identity), and there was no analytical verification of the actual concentrations (see Section 7.1).

The Environment Agency considers that the water solubility of PFiHx is probably **below 1 mg/L at 20 °C**, although there is uncertainty in the actual value. Ideally the water solubility should be measured using a standard method, taking care to minimise colloid formation and volatilisation. In the absence of better information, a water solubility of **0.1 mg/L at 25 °C** will be used in the assessment as a reasonable upper limit, based on the measured water solubility of the close analogue perfluorohexane (and supported by some *in silico* models).

5.4 Partition co-efficient (n-octanol/water; log K_{OW})

5.4.1 Measured data

An experimentally derived log K_{OW} of > 3.74 at 21.5 °C and pH 7 was presented in the EU REACH registration dossier of PFiHx (ECHA, 2020a). The study was performed using a shake flask method in accordance with OECD TG 107 (OECD, 1995b), and was GLP compliant. The EU REACH registration assessed the data reliability as Klimisch score 1 (reliable without restrictions).

The EU REACH registration provided octanol-water partitioning data on PFiHx in response to requests for further information made by the Environment Agency. A mixture of PFiHx, water and 1-octanol were shaken vigorously, then left to stand for 2 days. The mixture formed three layers, with 1-octanol at the top, water in the middle, and perfluoro-2-methylpentane at the bottom. The water and 1-octanol were then extracted and analysed by GC. K_{OW} was calculated from the solubility of PFiHx in 1-octanol and in water. The log K_{OW} of PFiHx was reported as >4.8. No indication of GLP or reliability of the study was provided. (Unpublished, 2021c).

5.4.2 Predicted data

The supporting information in the registration refers to a predicted log K_{OW} value of approximately 5.02 at 21.5 °C generated in the EU REACH registration using EPISuite™ (ECHA, 2020a). The EU REACH registration assessed the data reliability as Klimisch score 4 (not assignable). The Environment Agency generated a predicted value of log K_{OW} of 5.02 using KOWWIN v1.68 (US EPA, 2020c).

The ChemSpider database and US EPA CompTox dashboard contained estimated log K_{OW} values from EPISuite™, ACD/Labs and OPERA software (RSC, 2020a; US EPA, 2020a). Values are presented in Table 5.7 Predicted log K_{OW} values for PFiHx.

Table 5.7 Predicted log K_{OW} values for PFiHx

Model	Details	Log K_{OW}
ACD/Labs	ACD/LogP ACD/LogD (pH 5.5)	5.44 4.89
EPISuite™	KOWWIN v1.67 estimate	5.31
OPERA	Global applicability domain: Inside Local applicability domain index: 0.46 Confidence interval 0.433	3.8

In silico predicted values should always be treated with caution where substances in the training set and external test set are not visible.

- For the ACD/labs model this information was not available, therefore no assessment of the applicability can be performed.

- Guidance provided with the KOWWIN v1.67 model indicates that the relationship between the experimental and predicted values for a validation set of 10 331 compounds was good, with an R^2 of 0.94 and standard deviation of 0.47. The training set contained several PFCs (see Appendix B: QSAR models) including structurally similar substances of PFiHx (e.g. hexafluoroethane) and it is likely that the predicted value for PFiHx falls within the applicability domain of the model but the value should still be treated with caution.
- For the OPERA model, PFCs were included in both the training set and external test sets (e.g. perfluoropentane). PFiHx is considered inside the global applicability domain and has a local applicability domain index of 0.4 to 0.6 and therefore the prediction should be considered with caution.

5.4.3 Data from structural analogues

The Environment Agency has found data for perfluorohexane. PFiHx and perfluorohexane are isomers, so there is likely to be only a minor difference in log K_{OW} values[3].

A log K_{OW} value of > 4.5 at 20 °C is cited in the EU REACH registration of perfluorohexane (ECHA, 2020b). This was estimated in accordance with OECD TG 107 (OECD, 1995b) as the ratio of solubility in n-octanol (mean value ≥3.0 g/L) and water (≤ 0.1 mg/L). The source was an unnamed study report (2018) (ECHA, 2020b); the method was GLP compliant. The EU REACH registration gave the study a Klimisch score of 2 (reliable with restrictions).

For comparison, the ChemSpider database and US EPA CompTox dashboard contained estimated log K_{OW} values from EPISuite™, ACD/Labs and OPERA software (RSC, 2020b; US EPA, 2020b). Values are presented in Table 5.8.

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[3] For example, in the case of non-fluorinated hydrocarbons, data from ECHA's public dissemination website indicates that n-hexane, 2-methyl-pentane and hex-1-ene have a log K_{OW} of 4, 3.2 and 3.9 at 25 °C, respectively; no data are available for 4-methyl-pent-2-ene for comparison.

Table 5.8 Predicted log K_{OW} values for perfluorohexane

Model	Details	Log K_{OW}
ACD/Labs	ACD/LogP ACD/LogD (pH 5.5)	5.65 4.80
EPISuite™	KOWWIN v1.67 estimate	6.02
OPERA	Global applicability domain: Inside Local applicability domain index: 0.50 Confidence interval 0.45	3.75

5.4.4 Additional sources

Tsai (2009) estimated the log K_{OW} of several PFCs using a fragment constant approach as summarised below in Table 5.9 Summary of estimated log K_{OW} of perfluoroalkane analogues

Table 5.9 Summary of estimated log K_{OW} of perfluoroalkane analogues

Substance	Molecular weight (g/mol)	Log K_{OW}
Perfluoropentane	288	1.53
Perfluorohexane	338	1.79
Perfluoroheptane	388	2.05
Perfluorooctane	438	2.31
Perfluorononane	488	2.57

The Environment Agency notes that the predicted value for perfluorohexane is much lower than those estimated using other models. The reliability of these values is therefore highly uncertain but they indicate a general trend of increasing hydrophobicity with longer chain length PFCs.

5.4.5 Recommended value

The EU REACH registration indicates that the log K_{OW} is > 3.74 at 21.5 °C using the shake-flask method (ECHA, 2020a). Although considered to be “fully reliable” in the EU REACH registration, the Environment Agency notes that according to Chernyshev and Skliar (2014), PFCs such as perfluorohexane form colloids in water, which may involve “liquid droplets, vapour bubbles or a combination of both phases simultaneously” (see Section 5.3). The substance is likely to partition from water to air (see Section 6.2.2), so controls to limit losses due to volatility may also be required during measurement. Both factors complicate the measurement of log K_{OW} and the Environment Agency considers that the reported value may be unreliable. Ideally a log K_{OW} value should be estimated using measured data (either the ratio of solubility in water and in n-octanol, or back-calculated from either a reliable organic carbon-water partition coefficient or fish bioconcentration factor). A further measured log K_{OW} of PFiHx was reported as >4.8 in the EU REACH registration.

In silico predictions for the log K_{OW} of PFiHx were in the range 3.75 to 5.44 (US EPA, 2020a and RSC, 2020a), although the reliability of these values is unknown.

Data from the analogue perfluorohexane do not provide much useful supporting evidence – the reported measured log K_{OW} in the EU REACH registration is an unbounded estimate (>4.5 at 20 °C), and QSAR predictions are in the range 3.75 to 6.02. Given the issues around colloid formation and volatility for this type of substance, the measured result may not be fully reliable. Tsai *et al*. (2002) and Tsai (2009) predicted a log K_{OW} around 1.8, but the Environment Agency considers this to be unreliable.

There is significant uncertainty in the log K_{OW} of PFiHx. In the absence of better information, the Environment Agency recommends a **log K_{OW} of 4.5 at 25 °C** for modelling purposes (with a range of **4 to 5 for the purposes of sensitivity analysis in the exposure modelling**), based on the measured log K_{OW} of the close analogue perfluorohexane. Ideally, a more reliable bounded value (either measured using a suitable method or extrapolated from other data) is needed and the UK supplier is recommended to provide this and update their REACH registration dossier accordingly.

5.5 Octanol-air partition coefficient (K_{OA})

The log K_{OA} is a non-standard endpoint under REACH used to predict the partitioning behaviour of organic compounds between air and environmental matrices such as soil, vegetation, and aerosol particles (Meylan and Howard, 2005). It is also relevant for the assessment of bioaccumulation potential in air-breathing organisms (Section 6.3.2).

5.5.1 Measured data

No experimental log K_{OA} values were presented in the EU REACH registration (ECHA, 2020a).

5.5.2 Predicted data

The Environment Agency has estimated log K_{OA} values using the dimensionless Henry's Law constant (K_{AW}) of 4.62 (see Section 6.2.2) and a log K_{OW} value of 4.5 (see Section 5.4.5) ($K_{OA} = K_{OW}/K_{AW}$). The resulting log K_{OA} is -0.12 (see Section 5.5).

As noted in Section 5.4.5, there is uncertainty in the K_{OW} value. If a log K_{OW} value of 5 is assumed, the log K_{OA} would be 0.38 and if a log K_{OW} value of 4.0 is assumed, the log K_{OA} would be -0.62.

As there is also uncertainty in the K_{AW} value, the reliability of these derived K_{OA} values is unknown.

The US EPA CompTox dashboard contained predicted K_{OA} values for PFiHx generated from KOAWIN v1.10 and OPERA software (RSC, 2020a, US EPA, 2020a). These values are presented in Table 5.10:

Table 5.10 Predicted log K_{OA} for PFiHx

Source	Details	Log K_{OA}
EPISuite™ Estimation programme KOAWIN v1.10	Log K_{OA} (log K_{OW} used: 5.31 and K_{AW} used: 5.88 estimated) Log K_{OA} (experimental database): None	-0.566
OPERA	Global applicability domain: Inside Local Applicability domain index: 0.914 Confidence Interval: 0.760	0.556
Calculation	Calculated from log K_{AW} of 4.62 and a log K_{OW} value of 4.5 ($K_{OA} = K_{OW}/K_{AW}$)	-0.12

In silico predicted values should always be treated with caution where substances in the training set and external test set are not visible.

- For the KOAWIN v1.10 model, the values are estimated from either predicted or experimental K_{AW} and K_{OW} values sourced from HENRYWIN and KOWWIN respectively. Therefore, the reliability of the predicted K_{OA} for PFiHx is dependent on the reliability of HENRYWIN and KOWWIN and the presence of structural analogues in their respective data sets.
- For the OPERA model, no close structural analogues of PFiHx were included in the training and external test sets. PFiHx is considered inside the global applicability domain and has a high local applicability domain index (> 0.6), so the prediction can be considered reliable based on the OPERA model applicability domain criteria.

5.5.3 Data from structural analogues

There are no measured data for structural analogues.

5.5.4 Additional sources

No relevant references were identified in the literature search.

5.5.5 Recommended value

No log K_{OA} values were presented in the EU REACH registration dossier (ECHA, 2020a), although it is not a standard information requirement.

Predicted values from the open literature and derived by the Environment Agency suggest a log K_{OA} in the range -0.566 to 0.556, although the reliability of these predictions is uncertain. The Environment Agency does not consider it appropriate to choose a single value from the estimated data range. This is considered further in Section 6.3.2.

5.6 Dissociation constant

No experimental dissociation constants were presented for PFiHx in the EU REACH registration (ECHA, 2020a). It states that the substance “does not dissociate”. The Environment Agency agrees that a dissociation constant is irrelevant for PFiHx as it has no ionisable functional groups. It will remain as a neutral compound at environmentally relevant pH.

6 Environmental fate properties

The same comments about sources of data, reliability scoring and use of supplemental information apply as for Section 5.

6.1 Degradation

6.1.1 Abiotic degradation

6.1.1.1 Hydrolysis

In the EU REACH registration dossier, the hydrolysis study is waived due to the substance being highly insoluble in water (see Section 5.3.5) (ECHA, 2020a). The measured water solubility is below 1 mg/L, which is the threshold for the test in the OECD TG 111 (OECD, 2004a).

The Environment Agency agrees that the structure of the substance suggests that hydrolysis is unlikely to be a relevant degradation pathway.

6.1.1.2 Phototransformation in air

No relevant information is available in the EU REACH registration dossier. This is not an information requirement at the current level of supply.

Direct photolysis of a fully fluorinated carbon chain is expected to be very slow, with stability likely to be sustained for more than 1 000 years (Environment Canada, 2012).

The US EPA CompTox dashboard and ChemSpider database contained predicted photodegradation half-life values for PFiHx generated from AOPWIN v1.92 and OPERA software (RSC, 2020a, US EPA, 2020a). These values are presented in Table 6.1.

Table 6.1 Predicted photodegradation half-life values for PFiHx

Source	Atmospheric hydroxylation rate constant	Half-life (days)
EPISuite™ Estimation programme AOPWIN v1.92	0 cm^3/molecule-sec	-
OPERA	7.44 x 10^{-16} cm^3/molecule-sec Global applicability domain: Outside Local Applicability domain index: 0.521 Confidence Interval: 0.560	21 600[a]

Note: a – Calculated by the Environment Agency using the European Union System for the Evaluation of Substances (EUSES) (v2.03).

AOPWIN v1.92 predicts no indirect photodegradation as there is no photochemically reactive group in the molecule. *In silico* predicted values should always be treated with caution where substances in the training set and external test set are not visible.

- For the AOPWIN v1.92 model this information was not available, therefore no assessment of the applicability can be performed. It is not known whether the training set contained substances structurally similar to PFiHx.
- For the OPERA model, no close structural analogues of PFiHx were included in the training and external test sets. PFiHx is considered outside the global applicability domain and has a local applicability domain index of 0.4 to 0.6 and therefore the prediction should be considered with caution.

Ravishankara *et al.* (1993) calculated atmospheric half-lives for a number of PFCs, including the analogue substance perfluorohexane, based on laboratory experiments to determine the rate constant for a number of atmospheric reaction pathways: photolysis (at a wavelength of 121.6 nm), reaction with oxygen, hydroxyl and hydrogen radicals, and high temperature thermolysis. Aside from thermolysis, the methods were described in a previous article by the same research group, for which the Environment Agency can only obtain an abstract. Measurement of the hydroxyl rate constant was only made for carbon tetrafluoride, and the authors state that in the absence of another reaction pathway, they estimate that the value will be the same or lower for the remaining chemicals. The results were input to a two-dimensional atmospheric model (the model is published in a paper by Garcia & Solomon (1985) but the Environment Agency has only been able to obtain an abstract). The estimated atmospheric lifetime of all of the tested PFCs exceeded 2 000 years and was 3 100 years for perfluorohexane. Given that PFiHx is an isomer of perfluorohexane, a similarly long atmospheric lifetime would be expected. The paper by Ravishankara *et al.* (1993) is well described and reasoned. The Environment Agency considers the findings are plausible, even though a full review of the experimental methods has not been possible.

6.1.1.3 Phototransformation in water

No relevant information is available in the EU REACH registration dossier or the scientific literature.

6.1.1.4 Phototransformation in soil

No relevant information is available in the EU REACH registration dossier or the scientific literature.

6.1.2 Biodegradation in water

6.1.2.1 Measured data

In the EU REACH registration dossier, biodegradation of PFiHx was tested in one screening study dated 2005 (ECHA, 2020a). The study report is attached to the IUCLID dossier and has been reviewed by the Environment Agency.

Table 6.2 Summary of screening biodegradation studies

Method	Results	Reliability	Reference
OECD TG 310 (ready biodegradability: CO_2 in sealed vessels (Headspace Test))	Test substance -1% degradation after 28 days (CO_2 production)	Registrant: 1 (key study)	Unpublished (2005) cited in ECHA (2020a)

This was a modern ready biodegradation test performed according to OECD TG 310 and to GLP (OECD, 2014). The test was conducted using a PFiHx concentration of 93.4 mg/L (equivalent to the 20 mg C/L required in the test guideline), and sodium benzoate as a reference substance. Due to the volatility of PFiHx it was directly injected into the test vessels using a micro-syringe. Test solutions were contained in sealed vessels with a headspace-to-liquid ratio of 1:2. Biodegradation was assessed by measuring inorganic carbon in the headspace on days 0, 2, 4, 6, 8, 10, 14, 16, 20, 22, 24, and 28. Dissolved organic carbon (DOC) was also measured for the control and reference substance at the start and end of study.

The results for PFiHx indicate that no degradation occurred during the 28-day test (the negative value is a consequence of measured inorganic carbon levels in the test vessels being below the inorganic carbon concentration in the control vessels). The validity criteria were met, as the reference substance attained 73% mineralisation in 14 days (threshold 60%) and the toxicity control reached 37% in 14 days (threshold 25%). The results from the two replicates for PFiHx were consistent, and the level of inorganic carbon in the control vessels was very low at the end of the study (1%), indicating that the test was valid.

The EU REACH registration concluded that the substance was “not inherently biodegradable” (presumably in the absence of any biodegradation being observed). They consider that the study is reliable without restriction (Klimisch score 1). Based on the indicated level of mineralisation the Environment Agency agrees with this conclusion. The test method was appropriate given the volatility of the substance (see Section 6.2.2). It is noted that the study was performed significantly in excess of the estimated water solubility of PFiHx. This does not invalidate the study, although it could potentially limit substance bioavailability. Nevertheless, in the absence of any observed mineralisation, it is not considered a significant issue in this test. The Environment Agency agrees with the EU REACH registration’s reliability score for the study but recommends that more detail is added to the robust study summary, so that it reflects the study report (for example, being clear that the validation criteria were met).

Two further biodegradation tests are cited in the confidential Chemical Safety Report (CSR) appended to the EU REACH registration. No information is provided about these studies, other than stating that no biodegradation was observed. Based on the study report titles, neither study was performed using PFiHx. Without further information these data have not been considered further.

No simulation test is available, and the endpoint is waived in the EU REACH registration dossier as not being scientifically necessary, with the EU REACH registration stating that "given the inertness of PFCs, we can be sure that [PFiHx] will not biodegrade".

6.1.2.2 Predicted data

There is no relevant information is available in the EU REACH registration dossier.

The Environment Agency is not aware of a biodegradation QSAR for which PFiHx is within the applicability domain.

6.1.2.3 Data from structural analogues

In a modern ready biodegradation test performed in 2018 according to OECD TG 301F and GLP, 0% biodegradation of perfluorohexane was observed after 28 days (ECHA, 2020b). Results were calculated from oxygen uptake and the EU REACH registration considered the study to be reliable without restriction.

This result supports the outcome of the OECD TG 310 test performed using PFiHx (OECD, 2014).

6.1.2.4 Recommended value

The EU REACH registration considers PFiHx is not readily biodegradable and the Environment Agency agrees that there are valid data to support this conclusion.

6.1.3 Biodegradation in sediment

No relevant information is available in the EU REACH registration dossier; the endpoint is waived as not being scientifically necessary, with the EU REACH registration stating that "given the inertness of PFCs, we can be sure that [PFiHx] will not biodegrade".

6.1.4 Biodegradation in soil

No relevant information is available in the EU REACH registration dossier; the endpoint is waived in the EU REACH registration dossier as not being scientifically necessary, with the EU REACH registration stating that "given the inertness of PFCs, we can be sure that [PFiHx] will not biodegrade".

6.1.5 Summary and discussion of degradation

There are no measured abiotic degradation data for PFiHx in the EU REACH registration dossier. Based on its chemical structure, the Environment Agency considers hydrolysis will not be a significant degradation pathway. Based on analogy with perfluorohexane, PFiHx could have an atmospheric lifetime in excess of 3 000 years.

The EU REACH registration considers that PFiHx is not readily biodegradable and the Environment Agency agrees that there are valid data to support this conclusion. The absence of any mineralisation in the ready biodegradation screening test is in line with the expectation that PFiHx will not be significantly biodegraded due to its perfluorinated structure.

6.2 Environmental distribution

6.2.1 Adsorption/desorption

6.2.1.1 Measured data

There are no measured data in the EU REACH registration dossier, which states that measurement is extremely difficult due to the low water solubility and high volatility of PFiHx (ECHA, 2020a).

6.2.1.2 Predicted data

In the EU REACH registration dossier, 2 predictions of K_{OC} are provided using the QSARs in EPISuite^{TM}. The results are:

Log K_{OC} (Molecular Connectivity Index method) = 4.9

Log K_{OC} (K_{OW} method) = 4.4

No further information is provided. The Environment Agency has not been able to determine whether any PFCs are in the training set of the two QSARs. The help file for PCKOCWIN does not mention fluorinated substances in the fragment correction values, and in the available training sets fluorophenyl ureas are the only obviously fluorinated chemicals, which are not relevant for PFiHx. Without further justification, the Environment Agency does not consider the predictions to be valid as it is not known whether PFiHx is within the applicability domain.

The Environment Agency has predicted the log K_{OC} for PFiHx using the preferred log K_{OW} value of 4.5 (see Section 5.4.5). This was done in EUSES v2.03 using the “Predominantly hydrophobics” chemical class (the equation is: log K_{OC} = 0.81 log K_{OW} + 0.10). The calculated log K_{OC} was 3.7. There is uncertainty in the K_{OW} value, which is likely to lie in the log K_{OW} range of 4 to 5 (see Section 5.4); the log K_{OC} range could be 3.3 to 4.1 using the same equation.

According to the published paper for the QSAR (Sabljic *et al.*, 1995), it is suitable for chemicals containing fluorine (despite none of the 81 chemicals in the training set containing fluorine). The log K_{OW} value of PFiHx means that it is within the applicability domain of the model.

The US EPA CompTox dashboard and ChemSpider database contained predicted log K_{OC} values for PFiHx generated from KOCWIN v1.66 and OPERA software (RSC, 2020a, US EPA, 2020a). The Environment Agency has generated predicted K_{OC} values for PFiHx using KOCWIN v2.0 as ChemSpider does not report whether which method was used for the prediction. The values are presented in Table 6.3 Predicted log K_{OC} for PFiHx.

Table 6.3 Predicted log K_{OC} for PFiHx

Source	Details	log K_{OC}
EPISuite™ Estimation programme KOCWIN v1.66	It is unclear whether this prediction is based on the Molecular Connectivity Index method or on the Log K_{OW} method	5.01
EPISuite™ Estimation programme KOCWIN v2.0	Molecular Connectivity Index method K_{OC} = 7.95 x 10^4 L/kg	4.9
	Log K_{OW} method (estimated log K_{OW} = 5.02) K_{OC} = 2.27 x 10^4 L/kg	4.36
OPERA	Global applicability domain: Outside Local Applicability domain index: 0.455 Confidence Interval: 0.602	3.66
EUSES v2.03 model calculation from log K_{OW}	Log K_{OW} = 4.5 and 'predominantly hydrophobics" equation	3.7

In silico predicted values should always be treated with caution where substances in the training set and external test set are not visible.

- For the KOCWIN v2.0 model, the training and validation sets contained no PFCs (see Appendix B: QSAR models) and it is likely that the predicted value for PFiHx does not fall within the applicability domain of the model so the prediction is not considered reliable.

- For the OPERA model, no close structural analogues of PFiHx were included in either the training set or external test sets. PFiHx is considered outside the global applicability domain and has a local applicability domain index of 0.4 to 0.6 and therefore the prediction should be considered with caution.

6.2.1.3 Data from structural analogues

In the EU REACH registration dossier for perfluorohexane, the K_{OC} endpoint is fulfilled using a QSAR (a study using OECD TG 117 was attempted (OECD, 2004b), but as the substance could not be detected in the test, the results could not be used) (ECHA, 2020b). Using the equation Log K_{OC} = 0.81 log K_{OW} + 0.10, and a log K_{OW} value of ≥ 4.5, the EU

REACH registration calculated a log K_{OC} value of ≥ 3.7. The QSAR is the same one used by the Environment Agency to estimate the log K_{OC} of PFiHx, so similar caveats apply.

6.2.1.4 Recommended value

There is significant uncertainty in the log K_{OC} of PFiHx. In the absence of better information, the Environment Agency recommends a log K_{OC} of 3.7 at 25 °C for modelling purposes (with a range of 3.2 to 4.2 for the purposes of sensitivity analysis). The Environment Agency recommends that the robust study summary is updated to provide further information on reliability and consider other models (or a new measurement) if appropriate.

6.2.2 Volatilisation

6.2.2.1 Measured data

No measured data was presented in the EU REACH registration dossier (ECHA, 2020a).

6.2.2.2 Predicted data

In the EU REACH registration dossier, the Henry's Law constant (HLC) at 25 °C has been calculated as 1 840 atm m^3/mol (equivalent to 1.86 x 10^8 Pa m^3/mol). This is stated to have been estimated using “US EPA software”, but the QSAR is not specified. The Environment Agency has estimated this value as 18 400 atm m^3/mol (equivalent to 1.86 x 10^9 Pa m^3/mol) using HENRYWIN v3.10 (see Table 6.4) which is an order of magnitude greater than that presented in the EU REACH registration.

A HLC of 9.8 x 10^7 Pa m^3/mol was calculated by the Environment Agency using EUSES (v2.03) and the recommended values for water solubility (0.1 mg/L) and vapour pressure (29 kPa) at 25 °C (see Sections 5.3.5 and 5.1.5).

The US EPA CompTox dashboard and ChemSpider database contained predicted HLC values for PFiHx generated from OPERA software (RSC, 2020a; US EPA, 2020a). These values are presented in Table 6.4. The Environment Agency converted the values from atm m^3/mol to Pa m^3/mol.

Table 6.4 Predicted Henry's Law constant for PFiHx

Source	Details	HLC (Pa m³/mol)
EPISuite™ Estimation programme HENRYWIN v3.1	Bond Method: 1.84×10^{4} atm m³/mol Group Method: Incomplete	1.86×10^{9}
	Vapour pressure/water solubility estimate using EPISuite™ derived values: 2.59×10^{3} atm m³/mol	2.62×10^{8}
OPERA	Predicted value: 1.33×10^{-2} atm m³/mol Global applicability domain: outside Local Applicability domain index: 0.134 Confidence Interval: 0.312	1.35×10^{3}
EUSES	Calculated from water solubility of 0.1 mg/L at 25 °C and vapour pressure of 29 kPa at 25 °C	9.8×10^{7}

In silico predicted values should always be treated with caution where substances in the training set and external test set are not visible.

- For the HENRYWIN v3.1 model, the training and validation sets contained several PFCs (see Appendix B: QSAR models) and it is likely that the predicted value for PFiHx falls within the applicability domain of the model. However, the prediction relies on predicted values for vapour pressure and water solubility, so the output should be treated with additional caution.
- For the OPERA model, no close structural analogues of PFiHx were included in either the training set or external test sets. PFiHx is considered outside the global applicability domain and has a low local applicability domain index (< 0.4), so the prediction is not considered reliable based on the OPERA model applicability domain criteria.

6.2.2.3 Data from structural analogues

No relevant information is provided in the EU REACH registration dossier for perfluorohexane (ECHA, 2020b).

6.2.2.4 Recommended value

The Environment Agency recommends a HLC of **9.8×10^{7} Pa m^{3} mol^{-1}** for modelling purposes, calculated from the preferred water solubility value (0.1 mg/L) and vapour pressure (29 kPa), recognising that it is uncertain. It is within the range of predicted values using QSARs, although they may not be fully reliable. It suggests that the substance will tend to volatilise significantly from water.

This value has been used to derive the dimensionless HLC or air-water partition coefficient (log K_{AW}) of 4.62, which is used in modelling the long-range transport potential of PFiHx (see Section 6.2.4).

The Environment Agency recommends that the robust study summary is updated to provide further information on reliability and consider other models if appropriate.

6.2.3 Distribution modelling

Fugacity modelling predicts how a substance may be distributed in the environment following a release to a specific compartment (i.e. air, water or soil). The potential environmental distribution of PFiHx has been assessed by the Environment Agency using EPISuite^{TM} (US EPA 2020c, version 4.11) and is summarised in Table 6.5. This program contains a Level III multimedia fugacity model and predicts partitioning of chemicals to air, soil, sediment and water under steady state conditions for a generic model "environment". A fixed temperature of 25 °C is assumed. Mass transport between the compartments via volatilization, diffusion, deposition and runoff are modelled.

The model was run four times with a nominal release rate of 1 000 kg/hour initially entering the air, soil or water compartments and the same release to all three compartments using substance properties as summarised in Table 10.2.

Table 6.5 Results of generic level III fugacity model for PFiHx

Compartment (per cent distribution at steady state)	Emission rate (1 000 kg/h) to			
	air	water	soil	air: water: soil equally
Amount in air (%)	100.0	13.9	98.0	38.8
Amount in water (%)	<0.1	56.0	<0.1	39.6
Amount in soil (%)	<0.1	<0.1	2.0	0.3
Amount in sediment (%)	<0.1	30.2	<0.1	21.4

The modelling suggests that if PFiHx is released to the atmosphere it will remain there. If released to soil, it will also end up residing mostly in air. However, if released to water or air/water/soil in equal proportions, a significant fraction will remain in water (with potential transfer to sediment too).

The Environment Agency has used the SimpleTreat model in EUSES (v2.03) to predict the following partitioning of PFiHx in a wastewater treatment plant. The sensitivity of changing the log K_{OC} value is summarised in Table 6.6.

Table 6.6 Predicted partitioning of PFiHx in a wastewater treatment plant

Fraction of emission to compartment / degraded	Log K_{OC}		
	3.3	**3.7**	**4.1**
Air	80.2%	66.9%	51.2%
Water	4.4%	4.0%	3.6%
Sludge	15.4%	29.2%	45.2%
Biodegradation	0%	0%	0%

This model predicts that a significant fraction will partition to air and sludge, with a small fraction emitted to effluent. The reliability of this prediction for this type of substance is unknown, and the uncertainties in the physico-chemical input parameters also mean that this distribution might not be fully reliable.

6.2.4 Long-range transport potential

The EU REACH Guidance (Chapter R.7B, Section R.7.9.4.3) indicates that long-range transport can be considered on a case-by-case basis, but there is no guidance about how to use the information in the overall assessment.

The OECD has produced a decision support tool for estimating the long-range transport potential (LRTP) of organic chemicals at a screening level (OECD, 2009). It is a steady state non-equilibrium model in a standardised evaluative environment and predicts two characteristics that can be used to provide an indication of the LRTP of a substance: Characteristic Travel Distance and Transfer Efficiency. It also predicts overall persistence (POV). To estimate the LRTP of PFiHx, the Environment Agency has performed calculations using input parameters for PFiHx, as indicated in Table 6.7. The OECD LRTP screening tool allows comparisons of these three characteristics for a range of substances, provided in Figure 6.1 Long-range transport potential of PFiHx (log K_{OW} of 4.5).

Table 6.7 Estimated long-range transport potential of PFiHx

Input Parameter	Value		
Molecular mass	338 g/mol		
Log K_{AW} [a]	4.6		
Log K_{OW}	4.5 (range of 4.0 to 5.0)		
Half-life in air (hours)	2.4×10^{41}		
Half-life in water (hours)[b]	2.4×10^{41}		
Half-life in soil (hours)	2.4×10^{41}		
LRTP output parameter	Log K_{OW}		
	4.0	4.1	5.0
Characteristic Travel Distance (km)	1 350 000	1 350 000	1 350 000
Transfer Efficiency (%)	1 042	1 042	1 042
P_{OV} (days)	2.4×10^{40}	2.4×10^{40}	2.4×10^{40}

Note: a - This is the log of the dimensionless HLC calculated using Equation R.16-5 of REACH Guidance R.16 (ECHA, 2016) – see Section 7.2.2.

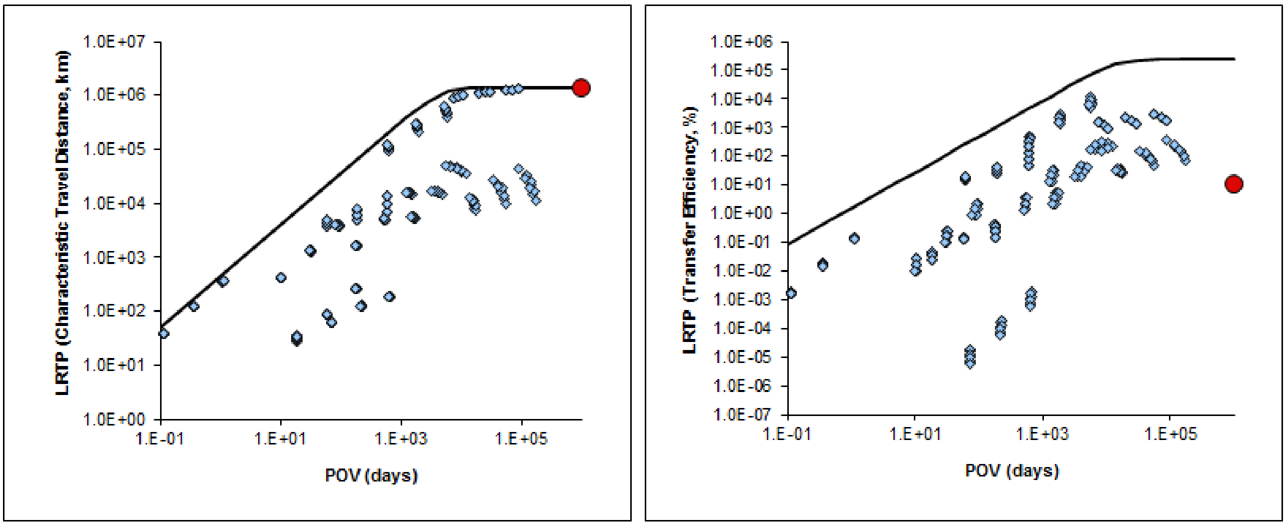
b -The upper bound value for biodegradation of a non-readily biodegradable substance in EUSES is 1×10^{40} days to represent infinity (equivalent to 2.4×10^{41} hours).

The OECD LRTP screening tool predicts the following outputs:

- Overall persistence (Pov).
- Characteristic Travel Distance (CTD): a transport-oriented LRTP indicator. It quantifies the distance from the point of release to the point at which the concentration has dropped to 1/e, or about 37% of its initial value; and
- Transfer Efficiency (TE): is a target-oriented LRTP indicator originally applied to quantify the deposition of chemicals transported from different regions to the North American Great Lakes.

The sensitivity of changing the log K_{OW} value over the range 4 to 5 was investigated but due to the very slow degradation rate used in the input parameters for air, water and soil compartments, there is negligible change in the output.

Figure 6.1 Long-range transport potential of PFiHx (log K_{OW} of 4.5)



Note: In the left hand graph the x axis is overall persistence in days (Pov) and the y axis is the Characteristic Travel Distance (km). In the right hand graph the x axis is overall persistence in days (Pov) and the y axis is the Transfer Efficiency (%).

Based on this screening tool, it appears that PFiHx may be capable of long-range transport.

Wet and dry deposition, which are important for the atmospheric fate of perfluorinated acids, are less relevant for PFiHx due to its different physico-chemical characteristics (PFiHx is considerably more volatile and less water soluble than PFAS such as perfluorooctanoic acid). Due to its low water solubility, removal of PFiHx from the atmosphere through precipitation is not likely to be a significant process and rainwater concentrations are likely to be low.

Evidence of occurrence (or not) of PFiHx in the Arctic and other remote regions also needs to be taken into account (noting the proximity of industrial activity and population centres). This is beyond the scope of this evaluation.

6.3 Bioaccumulation

6.3.1 Bioaccumulation in aquatic organisms

6.3.1.1 Screening data

The likely log K_{OW} of PFiHx (4.5, range 4 to 5; see Section 5.4.5) suggests that it screens as potentially bioaccumulative in aquatic organisms. For example, the ECHA guidance for environmental exposure assessment uses a threshold of log Kow ≥3 as a trigger for the secondary poisoning assessment (ECHA, 2016).

The analogue perfluorohexane has a relatively high solubility in n-octanol, which is a surrogate for lipid (≥ 3.0 g/L at 20 °C) (see Section 5.4.3). Although the reliability of these data are uncertain, it is possible that PFiHx might also have a high solubility in n-octanol, and therefore lipids by extension.

The Environment Agency has predicted a bioconcentration factor (BCF) for PFiHx for aquatic organisms using the preferred log K_{OW} value of 4.5. This was done in EUSES v2.03 using the “Predominantly hydrophobics” chemical class. The calculated BCF was 1 330 L/kg wet weight (ww).

As noted in Section 5.4.5, the Environment Agency recommends that the uncertainty in the log K_{OW} value should be addressed using sensitivity analysis. If a log K_{OW} value of 5 is assumed, the BCF would be 3 550 L/kg ww.

6.3.1.2 Measured data

There is no experimental study of fish bioaccumulation for PFiHx itself.

The EU REACH registration dossier (ECHA, 2020a) fills this endpoint through read-across of a study on perfluoroperhydrophenanthrene, which has a reported fish bioconcentration factor (BCF) up to 30. Very limited information is provided about the study, and there is also limited information in the EU REACH registration dossier of perfluoroperhydrophenanthrene itself. This substance has been evaluated by the Environment Agency (Environment Agency, 2023). One of the main issues is whether the two test concentrations in the study exceeded the water solubility of perfluoroperhydrophenanthrene, as an exact water solubility value is not available. Without this, it is not possible verify the reliability of the study. Furthermore, the study was performed to an old methodology, which reduces the confidence that can be placed on the results.

The justification for read-across provided in the EU REACH registration dossier is that “it is well established that saturated PFCs form a class of chemicals with very similar properties.” In the CSR, it is also stated that lower boiling [point] PFCs would be expected to have lower bioaccumulation values than perfluoroperhydrophenanthrene. No other justification is provided.

The Environment Agency notes that perfluoroperhydrophenanthrene (with 3 fused cyclic rings) is structurally quite different to PFiHx (which has a short linear chain). It is also a heavier molecule with larger dimensions. The Environment Agency is not convinced that it is an appropriate surrogate, so recommends that the robust study summary for this endpoint is updated using the ECHA RAAF (ECHA, 2017a) to provide greater clarity and take account of differences in physico-chemical properties (e.g. n-octanol solubility) and molecular size and dimensions. Noting the above, it is also important for the water solubility value of perfluoroperhydrophenanthrene to be confirmed to validate the bioaccumulation study, as without this any read-across is uncertain.

The assumption that hydrophobic and lipophilic interactions between compound and substrate (as modelled by the log K_{OW}) are the main mechanisms governing bioaccumulation behaviour may not be applicable for this type of substance due to the oleophobic character of the perfluorinated alkyl chain. Nevertheless, the Environment Agency notes that the close analogue perfluorohexane appears to have a high level of solubility in n-octanol, which is a surrogate for lipids. There is also some evidence from studies in mammals that PFCs may have a long elimination half-life, although no data appears to be available for PFiHx (see Section 6.3.2).

In the absence of better information, the Environment Agency considers that PFiHx screens as potentially bioaccumulative in aquatic organisms, based on a likely log K_{OW} of 4.5 (range 4 to 5).

6.3.2 Terrestrial bioaccumulation

The EU REACH registration has not assessed the potential for terrestrial bioaccumulation as this is not a standard information requirement at this tonnage band. However, for completeness, the Environment Agency has considered the available screening data since some PFAS can accumulate in air-breathing organisms through non-lipid mediated mechanisms.

6.3.2.1 Screening data

In terms of bioaccumulation in air-breathing organisms, the screening criteria are log K_{OW} >2 and log K_{OA} >5. With a proposed log K_{OW} of 4.5 for PFiHx (range 4 to 5) the log K_{OW} criterion is met. Section 5.5 discusses the available estimates for K_{OA}, which range from -0.566 to 0.556 with a value of -0.12 derived using a log K_{OW} value of 4.5. There is uncertainty in the log K_{OW} value, and the log K_{OA} may be higher (0.38) if a log K_{OW} value of 5 (which is the upper value in the range from the sensitivity analysis) is used. Nevertheless, these values suggest that PFiHx does not meet the screening criteria for bioaccumulation in air-breathing organisms.

There is no measured information on the bioaccumulation of PFiHx in earthworms.

The Environment Agency has predicted a BCF for PFiHx for earthworms using the preferred log K_{OW} value of 4.5. This was done in EUSES v2.03 using the “Predominantly hydrophobics” chemical class. The calculated BCF was 380 L/kg ww. The QSAR was derived from data on a small number of organochlorine compounds, so this value is likely to be unreliable.

6.3.2.2 Other information

No relevant information is available in the publicly available EU REACH registration dossier of PFiHx (ECHA, 2020a). In a general discussion of bioaccumulation in the CSR, a conference paper by Yamanouchi & Yokoyama (1975) is cited. These authors indicate that “PFCs are mainly expelled through expiration; the rate of elimination is related to the amount of given dose in the type of the first order equation and fairly to their vapour pressure, the higher, the more rapidly excreted."

The Environment Agency has not been able to locate this specific reference, but found other papers (e.g. Okamoto *et al.,* 1975; Yokoyama *et al*., 1975) which appear to cover research by the same group. The substances investigated in these two papers were perfluorodecalin, perfluoro-1-methyldecalin, perfluorotributylamine, perfluoro-N,N-diethylcyclohexylamine and 2H-nonaconsafluro-3,6,9,12-tetraoxo-5,8,11-methyl-pentadecane. None of these substances is a close analogue of PFiHx.

In the introduction of Okamoto *et al.* (1975), it is stated that "the long term retention of [PFCs] in body tissues has been the main impediment for their use as the substitute of blood." The Environment Agency does not know if there is any specific information on elimination half-life in mammals for PFiHx or close analogues. However, it appears that tissue retention cannot be ruled out as a possibility.

Additional information on some of these studies is included in Section 8.1.

6.3.3 Summary and discussion of bioaccumulation

There are no valid measured data for aquatic bioaccumulation for the substance itself. Based on screening data, the substance could be bioaccumulative in aquatic organisms.

Limited terrestrial bioaccumulation data are available, but these indicate that tissue retention in mammalian species cannot be ruled out as a possibility.

In the absence of better information, the Environment Agency recommends deriving BCF values using the QSARs in EUSES, where these are needed for exposure modelling purposes. These QSARs rely on log K_{OW}. Using the recommended log K_{OW} value (4.5), the aquatic BCF is predicted to be 1 330 L/kg ww. However, the BCF is predicted to be as high as 3 550 L/kg ww if a log K_{OW} value of 5 (which is the upper value in the selected range) is used.

7 Ecotoxicology

The same comments about sources of data, reliability scoring and use of supplemental information apply as for Section 5. Performance of aquatic toxicity tests may be difficult as PFiHx is a volatile liquid. Measures would be needed to limit volatilisation, and analytical monitoring would be required to ensure that test concentrations are adequately maintained.

7.1 Aquatic compartment (including sediment)

7.1.1 Fish

7.1.1.1 Short-term (acute) toxicity

The EU REACH registration (ECHA, 2020a) includes details of an acute fish toxicity study for a read-across substance. Further details on the read-across substance identity are not included.

Table 7.1 Summary of acute toxicity to fish

Method	Species	Analytical method	Results	Reliability (Klimisch score)	Reference
OECD TG 203 (static) To GLP	Rainbow Trout *Oncorhynchus mykiss* [a]	None	96-h EC_{50} >100 mg/L based on unverified nominal concentrations of unknown read-across source substance; mortality endpoint	Registrant: 1 (key study)	Study performed in 1989, cited in ECHA, (2020a)

Note: a Cited under previous name of *Salmo gairdneri*.

The EU REACH registration considers this study (Unnamed, 1989 cited in ECHA, 2020a) to be reliable without restriction (Klimisch 1) and the key study for this endpoint. The study tested *Oncorhynchus mykiss* (Rainbow Trout) in a semi-static system with daily renewal following OECD TG 203 and GLP. Details of the test substance identity and purity are not included.

Details on exposure solution preparation are not available although it is noted that they were prepared with the aid of a dispersant quoted as ‘50% w/w megaface F142-D’. Analytical verification does not appear to have been undertaken for fresh or expired treatments. Overall, it is not possible to verify the concentration of test substance that fish were exposed to.

It is unclear if a series of exposure treatments or a single limit concentration were used, or whether a relevant vehicle control was included. Details of test organism size, age and health are not available although it appears that general pH, temperature and dissolved oxygen parameters were suitable. Data to assess the control mortality validity criterion are not available although the >60% dissolved oxygen saturation criterion was met.

No mortalities were observed in the nominal 100 mg/L treatment and the 96-hour LC_{50} was considered to be >100 mg/L.

Given that the test substance identity is not available and information relating to test design (for example, exposure solution preparation and verification) is limited in the EU REACH registration, it is not possible for the Environment Agency to conclude whether the study is reliable or if the read-across is justified.

The Environment Agency recommends that further information Is provided to characterise the source chemical, improve the robust study summary (e.g. details on test design, test solution preparation and analytical verification) and justify read-across to PFiHx as the target substance using ECHA's RAAF (ECHA, 2017a) to provide greater clarity for this endpoint.

7.1.1.2 Long-term (chronic) toxicity

Long-term toxicity tests on fish are not available. The substance is registered at a supply level of 100 to 1 000 tonnes/year under EU REACH, and Annex 9 includes a long-term fish toxicity study as a standard information requirement at this level of supply. The EU REACH registration (ECHA, 2020a) refers to data waiving although no further details are available online. The Environment Agency recommends that the dossier is updated to either provide these data or include further information to support the data waiving.

7.1.2 Aquatic invertebrates

7.1.2.1 Short-term (acute) toxicity

The EU REACH registration (ECHA, 2020a) includes details of an acute toxicity to invertebrates study for a read-across substance. Further details on the read-across substance identity are not included.

Table 7.2 Summary of acute toxicity to invertebrates

Method	Species	Analytical method	Results	Reliability (Klimisch score)	Reference
OECD TG 202 (static) To GLP	*Daphnia magna*	No details	48-h EC_{50} >0.1 mg/L based on unverified nominal concentrations of unknown read-across source substance; mobility endpoint	Registrant: 1 (key study)	Study performed in 1989, cited in ECHA, (2020a)

The EU REACH registration considers this study (Unnamed, 1989 cited in ECHA, 2020a) to be reliable without restriction (Klimisch 1) and the key study for this endpoint. The study tested *Daphnia magna* in a static system following OECD TG 202 and GLP. Details of the test item identity and purity are not included.

Details on exposure solution preparation are not available although it is noted that they were prepared with the aid of a dispersant quoted as '50% w/w megaface F142-D'. Analytical verification does not appear to have been undertaken for fresh or expired treatments. Overall, it is not possible to verify the concentration of test item that fish were exposed to.

It is unclear if a series of exposure treatments or a single limit concentration were used, or whether a relevant vehicle control was included. Details of test organism and test design details such as replicates, feeding and media are not available although it appears that general pH and temperature parameters were suitable. Data to assess the control mortality or dissolved oxygen criteria are not available.

Based on immobilisation, the 48-hour EC_{50} was considered >0.1 mg/L.

Given that the test substance identity is not available and information relating to test design (for example, exposure solution preparation and verification) is limited in the EU REACH registration, it is not possible for the Environment Agency to conclude whether the study is reliable or if the read-across is justified.

The Environment Agency recommends that the further information is provided to characterise the source chemical, improve the robust study summary (e.g. details on test design, test solution preparation and analytical verification) and justify read-across to PFiHx as the target substance using ECHA's RAAF (ECHA, 2017a) to provide greater clarity for this endpoint.

7.1.2.2 Long-term (chronic) toxicity

Long-term toxicity tests are not available. The substance is registered at a supply level of 100 to 1 000 tonnes/year under EU REACH, and Annex 9 includes a long-term invertebrate toxicity study as a standard information requirement at this level of supply.

The EU REACH registration (ECHA, 2020a) refers to data waiving although no further details are available online. The Environment Agency recommends that the dossier is updated to either provide these data or include further information to support the data waiving.

7.1.3 Algae and aquatic plants

There are no data for toxicity to algae or aquatic plants in the EU REACH registration (ECHA 2020a). The endpoint is a standard information requirement at the current level of supply (100 to 1 000 tonnes/year) and appears to be waived in the EU REACH registration although there is no further information to support this. The Environment Agency considers this to be a data gap, and recommends additional information is provided in the dossier to either provide these data or support the data waiving.

7.1.4 Sediment organisms

No relevant information is available in the EU REACH registration dossier, but this is not a standard information requirement at the current level of supply (100 to 1 000 tonnes/year).

7.1.5 Other aquatic organisms

No relevant information is available.

7.2 Terrestrial compartment

No relevant information is available in the EU REACH registration dossier.

The substance is registered at a supply level of 100 to 1 000 tonnes/year under EU REACH, and Annex 9 notes that terrestrial toxicity testing may be required at this level of supply. The EU REACH registration (ECHA, 2020a) refers to data waiving although no further details are available online. The Environment Agency considers that further information should be included in the dossier to support the data waiving.

7.3 Microbiological activity in sewage treatment systems

The EU REACH registration (ECHA, 2020a) includes details of an Activated Sludge Respiration Inhibition Test (ASRIT) for a read-across substance. Further details on the read-across substance identity are not included.

Table 7.3 Summary of toxicity to sewage microorganisms

Method	Analytical method	Results	Reliability (Klimisch score)	Reference
OECD TG 209 (1984) To GLP	None	3-hour EC_{50} > 100 mg/L (nominal) based on unknown read-across source substance	Registrant: 1 (key study)	Study performed in 1989, cited in ECHA, (2020a)

The EU REACH registration considers this study (Unnamed, 1989 cited in ECHA, 2020a) to be reliable without restriction (Klimisch 1) and the key study for this endpoint. The study used a static system following OECD TG 209 (1984) and GLP. The latest OECD TG 209 document was published in 2010 (OECD, 2010). Details of the test item identity and purity are not included.

Activated sludge from a predominantly domestic wastewater treatment works was used although the loading rate is not presented. Details on exposure solution preparation are not available. Analytical measurement of the test item was not conducted (as this was not a requirement at the time the study was conducted).

It is unclear if a series of exposure treatments or a single limit concentration were employed and if a relevant vehicle control was included. Details of test design details such as replicates, temperature and confirmation of inocula source are not available although it appears that general pH was suitable.

A positive reference control (3,5-dichlorophenol) was included although a 3-hour EC_{30} is presented in place of a required 3-hour EC_{50}. Further details are not available to consider if this is a typographic error or if the 3-hour EC_{50} was within the expected range.

It is also unclear if validity criteria for the oxygen uptake rate and the coefficient of variation of oxygen uptake in the blank controls were met.

The 3-hour EC_{50} was considered > 100 mg/L based on the nominal initial concentration. A study no observed effect concentration (NOEC) is not presented.

Given that test substance identity is not available and information relating to test design (for example, exposure solution preparation, suspended solids concentration, and inhibition validity criteria) is not available in the EU REACH registration, it is not possible for the Environment Agency to conclude whether the study is reliable or if the read-across is justified.

The Environment Agency recommends that further information is provided to characterise the source chemical, improve the robust study summary (e.g. details on test design, solution preparation) and justify read-across to PFiHx as the target substance using ECHA’s RAAF (ECHA, 2017a) to provide greater clarity for this endpoint.

7.4 Atmospheric effects

The Environment Agency notes that the HLC for PFiHx indicates it is likely to partition to air (see Section 6.2.2). No data about biotic effects (e.g. to plants) from aerial exposure are available (ECHA, 2020a), although this is not a standard information requirement.

PFCs are known to be potent greenhouse gases, and this is considered further in Section 9.5.

8 Mammalian toxicology

The following information is taken directly from open literature and the public EU REACH registration for PFiHx (ECHA, 2020a). The focus is on those mammalian endpoints which are potentially relevant for determination of the substance as Toxic ('T') according to the REACH Annex 13 criteria (see Section 9.3) or for a wildlife secondary poisoning assessment. No human health hazard assessment has been undertaken. The study details and their reliability (Klimisch) scores are as presented in the EU REACH registration and the Environment Agency has not evaluated this information

Aside from some OECD genotoxicity studies, there are no standard regulatory studies on the registered substance itself. For each mammalian toxicology endpoint below, the EU REACH registration refers to a 'weight of evidence' case based on grouping of substances (category approach) or read-across to other PFCs.

8.1 Toxicokinetics

No toxicokinetics studies on the registered substance have been included in the EU REACH registration (ECHA, 2020a). The EU REACH registration mentions a read-across case based on "aggregated data from various published studies on PFCs" but the source substances are not named individually and few other details are provided. The case is largely based on the EU REACH registration's general assumption and experience that PFCs are not expected to be absorbed or metabolised in terrestrial mammals to any significant extent and will be excreted via the lungs.

Given the relevance of toxicokinetics to the bioaccumulation assessment (see Section 6.3.2), and because the EU REACH registration references a study by Okamoto *et al.* (1975) the Environment Agency performed a limited literature search for additional information. A brief summary is provided below noting that this information and its relevance to PFiHx has not been fully evaluated:

- Flaim (1994) states that intravenous PFC emulsions are cleared from the blood through a process involving phagocytosis of emulsion particles by reticuloendothelial macrophages (RES) and ultimate elimination through the lung in expired air. The rate of PFC elimination from the RES is proportional to the vapour pressure of the PFC, inversely proportional to molecular weight and positively influenced by lipophilicity. Dose-dependent respiratory excretion occurs with no evidence of metabolic products. Repeated administration of high doses of PFC emulsion may lead to a saturation of the RES-mediated clearance capacity, resulting in a redistribution of PFC to non-RES tissues.

  The Environment Agency notes that intravenous injection is not a relevant exposure route for organisms in the environment.

- Okamoto *et al.* (1975) measured the distribution and retention of 5 fluorochemicals in rabbits, rats and mice using a series of experiments. As noted in Section 6.3.2, a study by Okamoto *et al*. (1975) is referenced in the registration dossiers. Tests were performed as emulsions using 20% weight per volume (w/v) perfluorodecalin (FDC) and three different emulsifiers: 4% w/v Plauronic F-68 (described as a commercial polyoxyethylene-polyoxypropylene copolymer), 2% w/v egg-yolk phospholid and 2% w/v perfluorooctane-sulfonyl-amido-dimethylaminopropane-N-oxide (FNNO). The other substances were perfluorotributylamine, perfluoro-1-methyldecalin (FMD), perfluoro-N, N-diethylcyclohexylamine and 2H-nonacosafluoro-3,6,9,12-tetraoxa-5,8,11-methylpentadecane (Freon E4).

  The first experiment used male rabbits (species and breed not indicated) weighing 2.2 to 3 kg to test the effect of different emulsifiers on elimination time. The substance emulsion was injected into an ear vein, with a 4 g/kg bodyweight (bw) dose used for FDC. Blood samples (1 to 2 mL) were taken at 0, 6, 24, 48, 72 and 96 hours. Results are only reported as a graph in the paper and indicate that about 20% of FDC in the egg-yolk phospholipid emulsion remained after 96 hours in male rabbits compared to virtually complete elimination of FDC in the FNNO emulsion after 24 hours. The results are stated to be the mean of “at least 3 rabbits”. The authors suggest that the differences could result from different stability of the emulsions in the blood circulation.

  A second experiment investigated the effect of particle size of the emulsion on the elimination of the fluorochemical in rabbits using fine (average particle diameter 0.095 µm) and coarse (average particle diameter 0.3 µm) particles. The separation appears to have been done by using a centrifuge but this is not fully clear in the paper. This test used perfluorotributylamine, perfluoro-1-methyldecalin and Freon E4 (but not FDC) at a dose of 12 g/kg bw. The same animal weight and injection method as the first experiment were used. Results are reported in two graphs, which indicate that the finer emulsion was more slowly eliminated and accumulated less in the liver compared to the coarser one.

  A third experiment investigated the distribution of 3 fluorochemicals in rabbit organ tissue. This was performed using an injected dose of 12 g/kg bw using “at least 5 rabbits” per chemical, with the distribution assessed after one week. The same animal weight and injection method as the first experiment were used. Sixteen different tissues were analysed[4]. Only perfluorotributylamine, perfluoro-1-methyldecalin and Freon E4 appear to have been assessed (i.e. not FDC). The paper reports that similar results were seen for the chemicals with 40% of the

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[4] Brain, heart, lung, liver, spleen, kidney, adrenal, pancreas, small intestine, stomach, colon, femoral marrow, muscle, adipose tissue, bile and eyeball.

deposition occurring in the liver, spleen and lung. The highest concentrations were found in the spleen, femoral marrow and liver.

Based on the distribution in rabbits, a fourth experiment assessed the excretion of 3 of the substances from specific organs of mice over 8 weeks. This was conducted using male dd-strain mice weighing between 15 to 20 g and an injected dose of 4 g/kg bw (injection site not specified). Analysis was performed on the liver, spleen, lung and kidney of “at least 4 mice” at 48 hours, and 1, 2, 4 and 8 weeks. The results showed that FMD was the most quickly eliminated (FDC was not tested).

In a fifth experiment male Wistar rats weighing 200 to 250 g were used to compare the elimination of FMD and FDC from specific organs using an injected dose of 8 g/kg bw (injection site not specified). Concentrations were analysed in liver, spleen and lungs with measurements in “at least 5 rats” made at 1, 2 and 4 weeks. Results, based on the sum of the concentrations in the three organs, indicate 25% of FMC remaining after 1 week, 9% after 2 weeks and virtual elimination 4 weeks after injection. By comparison around 52-55% of FMD was detected at 1-2 weeks, with 31% after 4 weeks (21% and 10% in the liver and spleen).

The whole study concluded that of the substances tested, the elimination rate of FDC was the most rapid. The form of elimination was not investigated in this study, and instead the paper cites a second study by the authors (Yokoyama *et al.*, 1975), which is described below.

The Environment Agency notes that the Okamoto *et al.* (1975) study is very old, was not performed to a standard protocol and used a small number of animals. Nevertheless, it provides a useful insight into the possible target organs of perflurorodecalin, as well as an indication of the comparative rates of elimination. A half-life for perflurorodecalin cannot be reliably calculated from the rat experiment as it is unclear whether any substance was present in other parts of the rat which were not analysed (for example the rabbit experiment suggested bone marrow may be a significant target, but the elimination kinetics are unknown). One further aspect is the slower elimination of the egg-yolk phospholid emulsion. The relevance of this study to bioaccumulation assessment of PFiHx is considered further in Section 6.3.2.2.

- Yokoyama *et al.* (1975) studied the elimination rat of 6 fluorinated substances in male Wistar rats. These were perfluorotributylamine, perfluoro-1-methyldecalin, perfluoro-N,N-diethylcyclohexylamine, perfluoro-2-isopentylpyran, perflurorodecalin and perfluoro-N-methyldibutylamine. The total number of animals per chemical was not stated, but 8 to 10 rats were sampled at each time point. Animals weighing 140 to 160 g were injected in the tail vein with an emulsion of the PFC as a yolk phospholipid aqueous suspension (4 g/kg bw). Prior to injection the solutions had been filtered using a 0.45 µm filter to ensure that emulsion particle size was below this value (the paper indicates that the resulting average particle diameter was 0.1 to 0.2 µm). Depuration was studied over 14 days by measuring PFC concentration in urine, faeces and blood, the latter by sacrificing animals (and removing all blood). Samples were taken at 3 hours, and 1, 2, 4, 7 and 14 days. Chemical analysis was performed using GC, although the detection limits are not stated. Only perfluorotributylamine was detected in the urine and faeces during depuration, with all other chemicals detected solely in the blood. The measured half-lives were perfluorotributylamine (895.2 days), perfluoro-1-methyldecalin (109 days), perfluoro-N,N-diethylcyclohexylamine (62.4 days), perfluoro-2-isopentylpyran (38.2 days), perflurorodecalin (7.2 days) and perfluoro-N-methyldibutylamine (22.5 days).

The Environment Agency notes that the study is very old and was not performed to a standard protocol. Yokoyama *et al.* (1975) did, however, appear to use a larger number of animals than Okamoto *et al.* (1975). For perflurorodecalin, the half-life calculated is not whole body, but based on blood measurements alone, and it is not known whether the substance was present in other parts of the body. This said, the experiment does provide relative half-lives, and mathematically the half-life for perflurorodecalin cannot be below 7.2 days. The relevance of these studies to the bioaccumulation assessment of PFiHx is considered further in Section 6.3.2.2.

- A further cited article in some of the PFAS registrations from F2 Chemicals Ltd is Clark *et al.* (1975). The Environment Agency has been unable to obtain the full article. Based on the abstract this appears to be a review of perfluorinated substances as gas carriers (artificial blood). The abstract states that “perfluorinated substances … have reasonably short dwell times in the liver” but no further details are provided (the main issue appears to be restricting the use of high vapour pressure substances which can cause pulmonary gas embolism).

- Cabrales & Intaglietta (2013) state that PFC excretion has been an important consideration in their parenteral use (medical administration that is not oral). They note that the rate of *in vivo* excretion is principally determined by molecular weight (lower weight PFCs are more rapidly excreted).

- Chernyshev and Skliar (2014) (and references therein) state that saturated PFCs have unique properties including general biological inertness leading to a low level of toxicity, weak intermolecular interactions and high gas solubility, which have proved useful in biomedical applications. These include use as an ultrasound and magnetic resonance imaging contrast agent, blood substitute and propellant in inhalation drug delivery, for liquid ventilation and gene delivery applications, and as a means to enhance cavitation during ultrasound tissue ablation. These applications have presumably been associated with various clinical trials, with underlying toxicological information that has been evaluated by an appropriate regulatory authority. However, the Environment Agency has not identified any published reviews that summarise the findings.

8.2 Repeated dose toxicity

The EU REACH registration cites three repeated dose toxicity studies (ECHA, 2020a). These were not conducted on the registered substance but on perfluoroperhydrofluorene (CAS no. 307-08-4), perfluoropropane (CAS no. 76-19-7) and one unspecified substance. The EU REACH registration considers that these results can be read-across to the registered substance.

Table 8.1 Summary of mammalian repeated dose toxicity endpoints

Method and test substance	Species	Brief study details	Results	Reliability (Klimisch) score	Reference
Repeated dose toxicity: oral, 28-day (OECD TG 407). Conducted using perfluoroperhydro-fluorene To GLP	Rat	Administered daily via oral gavage in a limit test at 1 000 mg/kg bw/day (stated to be actual dose received) for 28 days.	NOAEL >1 000 mg/kg bw/day. The test material showed no significant toxic effect at a dosage of 1 000 mg/kg/day over 28 consecutive days.	Registrant: 1 (key study)	Study performed in 1988, cited in ECHA (2020a)
Short-term repeated dose toxicity: inhalation (no test guideline given). Conducted using perfluoropropane Not to GLP	Guinea pig	Exposure to ca. 10% perfluoro-propane in air for 10 days continuously	NOAEC >113 000 mg/m^3 (nominal). Some 'signs' noted but no significant adverse effects reported.	Registrant: 3 - Not reliable (key study)	Unnamed secondary source (1992) cited in ECHA (2020a)
Short-term repeated dose toxicity: dermal (no test guideline) Test substance unnamed No GLP compliance specified	Rat	Method not specified; animals were exposed continuously to an atmosphere containing the test material as 10% vapour for 10 days.	Some increases in weight and white blood cell count and histopathological changes noted in all dose groups - but overall the test material shows no significant adverse signs of repeated dose dermal toxicity.	Registrant: 4 - Not assignable (supporting study)	Unnamed secondary literature source (1992) cited in ECHA (2020a)

The Environment Agency notes that the relevance of one or more of these substances for PFiHx is uncertain. For example, perfluoroperhydrofluorene is a cyclic molecule with a higher molecular weight, and the identity of one of the substances is not provided.

Flaim (1994) states that the clearance mechanism for intravenous PFC emulsions from the blood (see Section 8.1) is characterised by dose-related stimulation of macrophages and subsequent release of intracellular products (particularly metabolites of the arachidonic acid cascade and cytokines) which are responsible for most of the biological effects associated with intravenous PFC emulsions (i.e. cutaneous flushing and fever at lower doses, and macrophage hypertrophy and recruitment at higher doses). These biological effects are reversible, and do not result in any permanent tissue alteration, even with prolonged exposure at relatively high doses. Repeated administration of high doses of PFC emulsion may lead to a saturation of the RES-mediated clearance capacity. This condition is benign with respect to the integrity of the surrounding parenchyma, as well as to the macrophages themselves. Increased pulmonary residual volume (IPRV) due to pulmonary gas (air) trapping, a reversible side effect, has been observed with intravenous doses of PFC emulsion in some animal species.

According to Flaim (1994), the gross morphological change associated with IPRV is not accompanied by any histological alteration other than the appearance of vacuolated macrophages (characteristic of the normal clearance mechanism) and some minor, increased inter-alveolar cellularity. Animal lungs affected by IPRV have a normal, pale pink appearance with no visible lesions or signs of oedema. The degree of IPRV is dependent on species, PFC dose, and type of PFC administered; PFCs with higher vapour pressures produce the most severe cases of IPRV in sensitive species. Species sensitivity depends upon physiological and morphological characteristics, but there is no evidence indicating that IPRV occurs in humans.

The Environment Agency does not know whether there are any more specific data on PFiHx or its close analogues.

8.3 Mutagenicity

The following information was provided in the EU REACH registration of PFiHx (ECHA, 2020a), once again involving an unspecified test substance.

Table 8.2 Summary of mutagenicity endpoints

Method	Species	Brief study details	Results	Reliability (Klimisch) score	Reference
Bacterial Reverse Mutation Assay (OECD TG 471). Test substance unnamed. To GLP	*Salmonella typhimurium* and *Escherichia coli* strains	Few details available	Substance does not cause genetic toxicity and has no ability to induce mutations under the test conditions	Registrant: 1 (key study)	Study performed in 2012, cited in ECHA (2020a)

8.4 Carcinogenicity

The EU REACH registration (ECHA, 2020a) includes the following information on perfluoropropane as a read-across substance for PFiHx.

Table 8.3 Summary of carcinogenicity endpoints

Method	Species	Brief study details	Results	Reliability (Klimisch) score	Reference
Mammalian Erythrocyte Micronucleus Test (OECD TG 474). Conducted using perfluoro-propane To GLP	Mouse	Singe oral gavage at 2 026 mg test material/mL to give total dose of 40 520 mg/kg. Bone marrow smears taken at 24, 48 and 72 hours examined for micronuclei and ratio of polychromatic to normochromatic erythrocytes	No toxic or genotoxic effects	Registrant: 1 (key study)	Study performed in 1984, cited in ECHA (2020a)

8.5 Toxicity to reproduction (effects on fertility and developmental toxicity)

The EU REACH registration for PFiHx does not contain any reproductive toxicity studies on the registered substance, but a weight of evidence and read-across case has been made based on an in-house summary review report (Unnamed, 2017, cited in ECHA, 2020a) referring to five other published references on PFCs. No reproductive or developmental toxicity effects were reported to occur in parental or offspring mammals at a NOAEL of up to 10 000 mg/kg bw/day (nominal).

The EU REACH registration states that this offers “good evidence that the substance is not toxic to reproduction, partly based on decades of use of this class of compound in medical applications, and therefore no testing is required”.

The validity of this claim has not been considered by the Environment Agency.

8.6 Summary of mammalian toxicology

Based on a weight of evidence and read-across approach, rather than any toxicity test results on the registered substance itself, the EU REACH registration does not identify any mammalian hazards for PFiHx. No Derived No-Effect Level (DNEL) is proposed. See Section 9.1 for further classification details.

The weight of evidence and read-across arguments, and reliability of the studies on the source substances, have not been evaluated by the Environment Agency.

9 Environmental hazard assessment

9.1 Classification and labelling

9.1.1 Harmonised classification

There is no current harmonised entry for PFiHx in Annex VI of the European Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008, nor a mandatory classification under GB CLP.

9.1.2 Self-classification

The EU REACH registration (ECHA, 2020a) has no self-classification for any hazards.

ECHA's Classification and Labelling (C&L) Inventory (https://echa.europa.eu/information-on-chemicals/cl-inventory-database accessed February 2021) aggregated self-classifications for PFiHx include the following hazard classes (ECHA, 2020c).

- STOT SE 3 (H335 lungs inhalation)

- Eye Irrit. 2 (H319)

- Skin Irrit. 3 (H315)

9.1.3 Conclusions for environmental classification and labelling

PFiHx is not readily biodegradable and there is no evidence that it degrades significantly via abiotic mechanisms (see Section 6.1). It is therefore considered to be "not rapidly degradable" for the purposes of hazard classification.

An aquatic bioaccumulation study is not available. The EU REACH registration has read across data from another substance to argue that the fish BCF is below 100, but the Environment Agency considers that additional arguments need to be made to support such a claim (see Section 6.3). The Environment Agency considers that the log K_{OW} of PFiHx is around 4.5 (range 4 to 5) at 25 °C. There is some uncertainty surrounding this value (see Section 5.4) as well as its relevance for assessing bioaccumulation potential for this type of substance (see Section 10.3). In the absence of a reliable fish BCF value and since the recommended log K_{OW} is greater than the CLP trigger of 4, the Environment Agency considers PFiHx to be potentially bioaccumulative for the purposes of hazard classification.

No short- or long-term aquatic toxicity data are available for PFiHx. Sufficient information is not currently available to support the proposed read-across of ecotoxicity hazard endpoints from short-term fish and invertebrate toxicity studies on other substances. No algal toxicity data are reported for either the substance or its analogues.

Noting that the substance is not rapidly degradable, is likely to have a low water solubility (0.1 mg/L or less) and has an indicative log K_{OW} >4, the Environment Agency considers that a ‘safety net’ classification of Aquatic Chronic 4 is appropriate. The Environment Agency therefore recommends that, in the absence of reliable acute and chronic aquatic toxicity data on the substance itself, or a suitable justification for not submitting these (e.g. in an updated REACH registration dossier), the UK supplier should update their self-classification from “no classification” to Aquatic Chronic 4.

Physical or human health hazard classifications for PFiHx have not been considered in this report.

9.2 Assessment of endocrine disrupting (ED) properties

The ecotoxicity data set does not include any studies that assess ED potential and no additional information was identified during the literature search (Appendix A: Literature search).

9.3 PBT and vPvB assessment

The EU REACH Registration for PFiHx (ECHA, 2020a) states that “the substance is not PBT/vPvB” with the following justification:

“[PFiHx] is an inert, volatile liquid, essentially insoluble in water. It is rapidly lost from water and soil by evaporation. Testing on perfluorocarbons for medical applications indicates they do not bioaccumulate, they are essentially harmless and they are rapidly lost from the human body”.

Further consideration by the Environment Agency in relation each of the REACH Annex 13 PBT/vPvB criteria is provided below.

<u>Persistence:</u> PFiHx is not readily biodegradable and there is no evidence that it degrades significantly via abiotic mechanisms (see Section 6.1).

PFiHx therefore meets the screening criterion for being potentially persistent (P) or very persistent (vP). No environmental half-life data for water, sediment or soil are available for comparison with the definitive criteria in REACH Annex 13 but, due to the stability of the saturated carbon-fluorine bonds, the Environment Agency considers it highly likely that the substance will be very persistent if released into the environment.

Distribution modelling suggests that the atmosphere may be an important sink (see Section 6.2). One study (Ravishankara *et al.,* 1993) estimates an atmospheric lifetime of

3 100 years for the analogue perfluorohexane. Given that PFiHx is an isomer of perfluorohexane, a similarly long atmospheric lifetime would be expected.

Bioaccumulation: There are no studies on the bioaccumulation of PFiHx in aquatic organisms for comparison with the definitive criteria in REACH Annex 13. As discussed in Section 6.3, there is significant uncertainty regarding the log K_{OW} of PFiHx and the Environment Agency proposes that a log K_{OW} of 4.5 (range 4 to 5) based on the measured log K_{OW} of the analogue perfluorohexane is used in the absence of more reliable information. The suggested log K_{OW} is the same as the REACH screening criterion (log $K_{OW} \geq 4.5$) for being potentially bioaccumulative (B). Given the uncertainty associated with this value, the Environment Agency believes it cannot be excluded that the substance meets the screening criterion for being potentially very bioaccumulative (vB) (log $K_{OW} \geq 5$). Based on a QSAR of uncertain reliability for this type of substance, the predicted fish BCF exceeds 2 000 L/kg ww. The Environment Agency also notes that the reported solubility of the analogue perfluorohexane in n-octanol (a surrogate for lipid) is ≥ 3 g/L, which suggests some capacity for this type of substance to partition into lipid-rich tissues.

In terms of bioaccumulation in air-breathing organisms, the screening criteria are a log $K_{OW} > 2$ and log $K_{OA} > 5$ (ECHA, 2017c). With a proposed log K_{OW} of 4.5 for PFiHx (range 4 to 5) the log K_{OW} criterion is met. However, the highest estimated log K_{OA} (0.556) is well below 5. There is substantial uncertainty regarding the derived K_{OA} values, but the data currently suggest that PFiHx does not meet the log K_{OA} screening criterion. However, additional information presented in Sections 6.3.2.2 and 8.1 indicate that retention in mammalian tissues (potentially through non-lipid mediated mechanisms) cannot be ruled out as a possibility.

Toxicity: In terms of aquatic toxicity, no data on PFiHx itself are presented in the EU REACH registration. An acute nominal 96-h EC_{50} of > 100 mg/L for Rainbow trout and nominal 48-h EC_{50} of > 0.1 mg/L for *Daphnia magna* are reported in Section 7, but these are based on unknown read-across source substance(s), with no reported analytical verification of exposure concentrations. There are also no algal toxicity data and no chronic fish or aquatic invertebrate data. At present there is no reliable information to determine whether the REACH Annex 13 criterion for ecotoxicity (T) of a NOEC of < 0.01 mg/L, or the acute screening criterion for being potentially 'T' ($L(E)C_{50} < 0.1$ mg/L), is met.

In terms of mammalian toxicology, no data are available in the EU REACH registration on PFiHx itself. Instead various weight of evidence and read-across proposals have been made based a broad category approach and some information on perfluoropropane (Section 8). The EU REACH registration does not identify any human health hazards for PFiHx. Self-classifications made under CLP do not meet the T criterion either (Section 9.1). However, the suitability of the weight of evidence and read-across arguments presented have not been considered by the Environment Agency at this stage.

No avian toxicity data are available but this is not a standard requirement for substances at this level of supply.

No information is available on the ED potential of PFiHx.

Overall conclusion: PFiHx screens as P/vP, and is likely to be extremely persistent in the environment. It screens as potentially B, and it cannot be ruled out that it screens as potentially vB. There is currently insufficient information to make a conclusion for T.

9.4 Groundwater hazard

Draft persistence, mobility and toxicity (PMT) criteria have been developed by the German Federal Environment Agency as intrinsic hazard criteria to identify substances that are difficult to remove during normal wastewater treatment practices and may be a threat to remote aquatic environments and drinking water sources, including groundwater (Arp and Hale, 2019). The criteria for P and vP are consistent with those in REACH Annex 13, whereas the mobile criterion is unique to PMT assessments. The draft T criteria include those in REACH Annex 13, in addition to considerations for carcinogenicity, effects via lactation, long-term toxicity to the general human population and ED potential.

There is no legal basis for these criteria under the REACH Regulation, but for completeness, a brief evaluation is included here.

Persistence: PFiHx meets the screening criterion for being P or vP (see Section 9.3).

Mobility: An experimental log K_{OC} value is not available. The Environment Agency suggests that a log K_{OC} of 3.7 (range 3.3 to 4.1) can be used as an approximation (see Section 6.2.1). PFiHx would therefore meet the draft criterion as being mobile (M) (log K_{OC} ≤ 4). A definitive log K_{OC} value is not available from a relevant soil study, so there is some uncertainty in this assessment.

Toxicity: There is insufficient information to make a conclusion for T (see Section 9.3).

Overall conclusion: PFiHx screens as P/vP, and is likely to be extremely persistent in the environment. It screens as potentially M. There is insufficient information to make a conclusion for T.

PFiHx is a relatively volatile liquid, and the influence of volatility is not considered under the draft PMT criteria.

9.5 Greenhouse gas hazard

Many fluorinated gases have very high global warming potentials (GWPs) relative to other greenhouse gases, so small atmospheric concentrations can have disproportionately large effects on global temperatures (US EPA, 2020d). In 2010, fluorinated gases covered under the Kyoto Protocol (F-gases) accounted for 2% of total anthropogenic greenhouse gas emissions (IPCC, 2014) and PFCs contribute to this.

The GWP is defined by the Intergovernmental Panel on Climate Change (IPCC, 2014) as "an index measuring the radiative forcing following an emission of a unit mass of a given substance, accumulated over a chosen time horizon, relative to that of the reference substance, carbon dioxide (CO_2). The GWP thus represents the combined effect of the differing times these substances remain in the atmosphere and their effectiveness in causing radiative forcing." Greenhouse gas emissions for PFCs are quantified as CO_2-equivalent emissions (in gigatonnes) ($GtCO_2$-eq) using weightings based on the energy absorbed by a gas over 100 years (the 100-year GWP). PFCs in the homologous series relevant to PFiHx are listed in Table 9.1. Their GWP values are sourced from the Fifth Assessment Report of the IPCC (IPCC, 2014). PFiHx is not included, but it is a structural isomer of perfluorohexane which is included (in ***bold italics***).

The Ozone-Depleting Substances (ODS) Substances and Fluorinated Greenhouse Gases (F-gas) Regulations quotes a GWP for perfluorohexane of 9 300 $GtCO_2$-eq which is higher than that reported by the IPCC (2014).

Table 9.1 Global warming Potential of PFCs

Perfluoroalkane	Trade name	Atmospheric lifetime		GWP (100 years) as CO_2 equivalent
		years	days	
Tetrafluoromethane	PFC14	50 000	-	6 630
Perfluoroethane	PFC116	10 000	-	11 100
-	PFC-c216	3 000	-	9 200
Perfluoropropane	PFC-218	2 600	-	8 900
Perfluorocyclobutane	PFC-318	3 200	-	9 540
Perfluorobutane	PFC-31-10	2 600	-	9 200
Perfluoropentane	PFC-41-12	4 100	-	8 550
Perfluorohexane	***PFC-51-14***	***3 100***	***-***	***7 910*** [a]
Perfluoroheptane	PFC-61-16	3 000	-	7 820
Perfluorooctane	PFC-71-18	3 000	-	7 620
Perfluorodecalin	PFC-91-18	2 000	-	7 190

Note: a - The IPCC Fourth Assessment Report gave a 100-year GWP of 9 300 $GtCO_2$-eq (Forster *et al.* 2007).

The IPPC (2013) contains insufficient methodological detail to allow the GWP for other PFCs to be calculated. However, as PFiHx is simply an isomer of perfluorohexane with no additional functional groups, the Environment Agency considers PFiHx will likely have a similar 100-year GWP (i.e. in the order of 8 000 $GtCO_2$-eq).

A qualitative risk characterisation for the atmosphere is included at Section 11.3.

9.6 Limit values

9.6.1 Predicted No Effect Concentration (PNEC) derivation

A PNEC is an indication of an acceptable environmental concentration based on evidence from (eco)toxicity studies.

Available hazard data are discussed in Sections 7, 8 and 9. The EU REACH registration considers the substance to be non-hazardous and has not derived PNECs. The Environment Agency considers that the substance should be classified for aquatic hazard in the absence of reliable information (see Section 9.1.3), which would oblige the UK supplier to perform an exposure and risk assessment under UK REACH. The Environment Agency notes however that the available public information is currently insufficiently detailed to allow the derivation of environmental PNECs following the REACH guidance (ECHA, 2008b). The Environment Agency therefore recommends that further supporting information is provided in the REACH registration dossier relating to the ecotoxicity and mammalian toxicology endpoints, so that a firmer judgement can be made about the need for derivation of PNECs - and also DNELs for human health risk assessment.

9.6.2 Qualitative/semi-quantitative descriptors for other critical hazards

As noted in Section 9.5, the substance may contribute to global warming, which could be considered a qualitative hazard.

10 Exposure assessment

A CSR was available in the EU REACH registration dossier, but since PFiHx is not (self-)classified by the UK supplier as hazardous, no assessment of environmental exposure was performed. The Environment Agency considers that, in the absence of more reliable information, the substance should be classified for environmental hazards (see Section 9.1.3). The Environment Agency has therefore prepared an environmental exposure assessment based on information in the EU REACH registration dossier, the environmental permit and information provided on the Registrant's website. This has been done to help decide on the priority for further work – it does not affect the company's responsibilities to demonstrate safe use for their substance.

10.1 Environment

10.1.1 Short description of emission scenarios and measures for reducing emissions to the environment

PFiHx is manufactured at a single UK site (F2 Chemicals Ltd, Lea Lane, Lea Town, Preston, Lancashire PR4 0RZ) in the range of 100 to 1 000 tonnes/year.

No other registered uses are mentioned in the EU REACH registration dossier, but the company's website suggests that it has a variety of applications, including in the electronics industry, as a heat transfer fluid, in rigid foam blowing and as a tracer and taggant (see Section 3). The Environment Agency does not have information on the tonnage split between these uses. Consumption by UK businesses is also likely to be significantly lower than the EU level of supply.

10.1.1.1 Routes of emission to surface water

There are no direct releases to surface water or groundwater at the manufacturing site, based on the environmental permit information and use pattern. Emissions to wastewater are noted as being from 'spent scrubber liquors, rainwater from the scrubber and DHF (dilute hydrofluoric acid) areas'. The total effluent emissions are estimated at 20 m^3/day which primarily comprises 'wash-down from production vessels and spent scrubber liquors'. There is no on-site treatment, and the effluent is discharged off-site to a municipal sewage treatment plant at Clifton Marsh.

There may be some potential for release to wastewaters or direct to surface waters in some of the substance's applications (e.g. tracers), but no information is currently available.

10.1.1.2 Routes of emission to land

There are no direct releases to soil at the manufacturing site, based on the environmental permit information and use pattern.

No information is currently available about potential routes of emission to land from the use of the substance.

10.1.1.3 Routes of emission to air

According to the company's environmental permit, environmental releases can be expected to be primarily to the air compartment. The company reports (total) releases of volatile organic compounds – assumed to be PFCs – in the region of 6 tonnes/year to air although the identity and quantity of individual substances is not stated.

Given that PFiHx is a volatile liquid, there may be some potential for direct release to air in some of the substance's applications (e.g. rigid foam blowing) and indirect release to air following emissions to wastewater, but no information is currently available.

10.1.2 Release assumptions made by the Environment Agency

The Environment Agency has received actual production volume data from the UK supplier. However, for the purposes of this evaluation, it can be assumed as an extreme worst case that PFiHx could be produced at up to 400 tonnes/year, which is the maximum capacity of the plant (see Section 3; this is stated to be for all products so is unlikely to be realistic). In the absence of detailed information on tonnage splits and releases for downstream uses, it is not appropriate to consider other parts of the life cycle for the time being.

The environmental release fractions for the Environmental Release Category (ERC) for manufacture can be based on the default worst case assumptions in the R.16 Guidance Document (ECHA, 2016), as summarised in Table 10.1 Uses and environmental releases for F2 Chemicals use only.

Table 10.1 Uses and environmental releases for F2 Chemicals use only

Use Type and ERC	Environmental release fraction used in the exposure assessment			Regional volume of use (tonnes /year)	Fraction of main local source	Number of emission days/year (local)
	to air	to wastewater	to soil			
ERC1: Manufacture of the substance	0.05	0.06	0	400	1	100[a]

Note: a - This is the default emission rate for the 100 – 1 000 tonne supply band in the R.16. Guidance Document (ECHA, 2016).

The adoption of these highly conservative assumptions indicates a worst case emission from the manufacture of PFiHx of 20 tonnes/year to air and 24 tonnes/year to wastewater for both local and regional scales. However, this essentially assumes that there is no abatement on site. The Environment Agency notes that:

- The site reports total PFC emissions of 6 tonnes/year to air. Given the registered tonnage bracket, the Environment Agency anticipates that PFiHx could comprise a large proportion of these emissions. A reasonable worst-case assumption is therefore that the emission to air from PFiHx is 6 tonnes/year at the local and regional scale (i.e. PFiHx accounts for all of the reported emission to air). This is equivalent to a release factor of 1.5% assuming a production volume of 400 tonnes/year.
- The site permit does not require wastewater emissions to be reported. Given the ratio of the reported and estimated air emissions (which differ by a factor of 3.3), a more realistic reasonable worst case release to wastewater might be in the region of 7 tonnes/year for the local and regional scales based on the extreme worst case tonnage. However, the Environment Agency notes that the Registrant/UK supplier has said that emissions to wastewater are “negligible”. For the purposes of this assessment, zero release to wastewater is assumed for this site, but the Environment Agency recommends that they explain the basis for their statement.

10.1.3 Predicted Environmental Concentrations (PECs)

Chemical concentrations can be predicted for various environmental compartments by inputting the environmental releases mentioned in Section 10.1.2 to the EUSES computer program (v2.0.3) (ECHA, 2020d). This is the best model currently available for assessing environmental exposure of novel chemicals in a standardised way.

In the following discussion, the 'local' environment is considered to be an area close to a site of release (e.g. the manufacturing site). The 'regional’ PEC is a background concentration arising from direct emissions of the substance from industrial processes and diffuse emissions as a consequence of the use of end products within a highly developed region, 200 km × 200 km in area, with 20 million inhabitants. The 'regional' scenario is equivalent to around 31% of the land area (130,279 km²) and 36% of the population (approximately 56 million people https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019) of England (the equivalent figures for the UK are around 16% for land area and 30% for population). The continental environment is the size of the EU and is generally used for mass balance purposes. The assessment is generic, representing a realistic worst case approach for a hypothetical environment that broadly reflects average European conditions. It is not intended to represent any specific part of the UK, with the exception of the local environment.

The key properties of PFiHx used in the EUSES calculations are summarised in Table 10.2 Substance-specific input parameters for the EUSES model. Unless stated otherwise, all other partitioning coefficients are derived using the log K_{OW} using the hydrophobic QSAR contained within the model (see Section 6).

Table 10.2 Substance-specific input parameters for the EUSES model

Parameter	Values used in this evaluation
Physical state	Liquid
Molecular weight, g/mol	338
Vapour pressure at 25 °C, kPa	29
Water solubility at 25 °C, mg/L	0.1
Octanol-water partition coefficient (log K_{OW})	4.5
Chemical class for K_{OC}-QSAR	Predominantly hydrophobics
Organic carbon-water partition coefficient (log K_{OC})	3.7
Suspended matter–water partitioning coefficient (log K_{SP})	2.7
BCF_{fish} (L/kg ww)	1 330
$BCF_{earthworm}$ (L/kg ww)	380
Half-life for degradation in air, hours	2.4×10^{40} $k_{OH} = 0$ cm^3/molecule/s
Biodegradability	Not readily biodegradable
Sewage treatment works removal rate:	

Parameter	Values used in this evaluation
Air Sludge	66.9% 29.2%

10.1.3.1 Air

The local air compartment is assumed to receive emissions from the process and via volatilisation from a wastewater treatment plant (WWTP) serving the site. The local PEC for air is estimated to be 1.64 mg/m^3 for the manufacturing site, representing the concentration at 100 metres from the emission source. The regional PEC is the same value as there is one source of emission in the region.

10.1.3.2 Other compartments

In the absence of any emission to a WWTP, no PECs for the aquatic (surface water and sediment) or soil compartments, groundwater or secondary poisoning have been derived.

The deposition of PFiHx from the atmosphere to surface media is not predicted to be a significant pathway due to its low water solubility and high vapour pressure. Therefore, PECs for PFiHx in water, sediment, soil and biota are expected to be very low.

10.1.4 Monitoring data

No monitoring data were identified in the EU REACH registration, academic literature or internal Environment Agency monitoring network.

10.1.5 Discussion

The derivation of the modelled PECs is influenced by a range of uncertainties including:

- Emission uncertainty (use pattern, emission scenarios and volumes);
- Parameter uncertainty (predicted physico-chemical and fate inputs, dilution factor);
- Modelling uncertainty (modelled WWTP removal); and
- Monitoring data uncertainty (no measurements available).

In the absence of more detailed information regarding emissions, use pattern and measured environmental concentrations, there remains significant uncertainty in this assessment. Therefore, this assessment is considered indicative of potential release and exposure of PFiHx in the environment.

Further refinement would be required to improve the reliability of this assessment. This could include specific information on UK tonnages, uses and releases, monitoring data and more reliable experimental data for physico-chemical properties.

11 Risk characterisation

11.1 Risks to aquatic and terrestrial compartments

No relevant environmental PNEC values are currently available to perform a risk characterisation using the PECs derived in the exposure assessment (although no PECs have currently been determined for fresh or marine surface water and sediment, groundwater, soil or relating to secondary poisoning).

11.2 Risks to human health via the environment

In the current absence of relevant human health hazards, a risk characterisation exercise is not considered for PFiHx.

11.3 Risks to the atmosphere

The Environment Agency considers PFiHx to have a significant global warming potential, with a 100-year GWP in the order of 8 000 GtCO$_2$-eq. (see Section 9.5). However, PFiHx is not one of the PFCs currently listed in the Ozone-Depleting Substances (ODS) Substances and Fluorinated Greenhouse Gases (F-gas) Regulations, although its analogue perfluorohexane is named there.

The Environmental Permitting Regulations require applicants to assess the GWP of their site emissions, but as long as Best Available Techniques are being used to control emissions, there is no requirement to reduce emissions in response to the site's GWP. The maximum emission of PFiHx from the manufacturing site is assumed to be 6 tonnes/year as a worst case (see Section 10.1.1). This would be an equivalent emission of CO$_2$ of 48 000 tonnes[5] using the CO$_2$ equivalent.

Emissions from other uses within the UK have not been considered due to lack of information. This is an information gap. However, given the physico-chemical properties of PFiHx, it seems plausible that most of the production volume (up to a theoretical maximum of 400 tonnes/year) could eventually end up in the atmosphere (unless specific measures are taken to recycle or destroy waste). The Environment Agency notes that some potential downstream user industries (e.g. the semi-conductor industry) have exemptions from some F-gas controls.

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[5] https://www.gov.uk/guidance/calculate-the-carbon-dioxide-equivalent-quantity-of-an-f-gas

12 Conclusion and recommendations

12.1 Conclusion

PFiHx is a branched perfluoroalkane, containing only carbon and fluorine atoms. It is a volatile liquid at standard temperature and pressure.

It is manufactured at a single UK site for use as a heat transfer fluid in the electronics industry and is also used in rigid foam blowing and as a tracer/taggant. Releases occur to air during manufacture up to a level of around 6 tonnes/year (although the actual amounts may be lower). Small releases may occur at downstream user sites (both to air and wastewater), although this has not been quantified.

Based on the available hazard data the following conclusions can be reached:

- PFiHx is not readily biodegradable and there is no evidence that it degrades significantly via abiotic or biotic mechanisms. It is considered likely to be very persistent (vP), with a long atmospheric half-life.
- There are no valid aquatic bioconcentration data for PFiHx itself but log K_{OW} estimates and other information indicate it screens as potentially bioaccumulative or very bioaccumulative.
- The EU Registrant does not self-classify the substance for any hazard, but information on its (eco)toxicity is currently inconclusive as there are no data on the substance itself. The Environment Agency recommends that a ‘safety net’ Aquatic Chronic 4 classification is applied.
- Further information is needed to determine its potential for bioaccumulation and (eco)toxicity before a PBT assessment can be concluded.
- PFiHx screens as P/vP and M but there is insufficient information to conclude whether it meets the T criterion. It might pose a concern regarding the contamination of groundwaters, although the influence of volatility is not considered in this assessment.
- No aquatic or terrestrial risk assessment has been performed due to insufficient information to determine appropriate PEC or PNEC values.
- An exposure modelling assessment has identified that there are likely to be direct emissions of PFiHx to the atmosphere. Available information suggests it also has the potential for long distance transport. Further usage and emissions information would be needed to refine this assessment. No data about biotic effects (e.g. to plants) from aerial exposure are available. Although not specifically named in the F-gas Regulations, it is a structural analogue of an identified greenhouse gas (perfluorohexane) and therefore is likely to present the same risk to the environment once emitted to the atmosphere.

12.2 Recommendations

12.2.1 Recommendations to the UK supplier

Although this evaluation is not a formal assessment under UK REACH, the Environment Agency proposes several ways to improve the data package to allow a more robust assessment of the hazards, exposure and risks posed by PFiHx:

- Details should be provided of appropriate analytical methodology for measuring PFiHx (and related PFC) emissions to air (see Section 2.1).
- Further detail should be added to the robust study summaries (RSS) relating to:
    - vapour pressure (Section 5.1)
    - surface tension, noting this should be measured in aqueous solution (Section 5.2)
    - water solubility, noting this should preferably be measured using an appropriate standard method, taking care to minimise colloid formation (Section 5.3)
- An update to the RSS and clarification of the log K_{OW}, noting this should ideally be estimated using measured data (either the ratio of solubility in water and in n-octanol, or back-calculated from either a reliable organic carbon-water partition coefficient or fish bioconcentration factor) (Section 5.4).
- Further detail in the RSS relating to the measured ready biodegradation screening test, including information on the test methodology, controls used and to confirm its validity (Section 6.1.2).
- Information to clarify the estimated log K_{OC}, noting this is based largely upon the log K_{OW}, so if further information is supplied to clarify that value, then further consideration should be given to the calculated log K_{OC} (Section 6.2.1).
- Information to clarify the Henry's Law constant, noting the current estimated value is based on a water solubility value of 0.1 mg/L. If it is proposed to alter this water solubility value then the Henry's Law constant should also be recalculated, unless directly measured (Section 6.2.2).
- Further information to justify read-across from the measured fish bioaccumulation study on perfluoroperhydrophenanthrene to PFiHx. This should take account of the guidance in ECHA's RAAF (ECHA, 2017a) and in Chapter 5 of the guidance on REACH information requirements relating to QSARs and grouping of chemicals (ECHA, 2008a). This should consider differences in physico-chemical properties (e.g. n-octanol solubility) and molecular size and dimensions of the source and target substances. The RSS should also be updated to clarify the water solubility of the source substance and to validate the bioaccumulation study, as without this any read-across is uncertain.
- Further detail in the RSS relating to short-term (acute) ecotoxicological endpoints for fish, aquatic invertebrates and sewage treatment microorganisms, together with further information to justify the read-across taking account of the guidance in ECHA (2017a and 2008a) (Section 7). It is also recommended that any data waivers for algae and long-term (chronic) ecotoxicological endpoints for fish and aquatic invertebrates are

more clearly justified, in accordance with ECHA's guidance on adaptation of long-term aquatic toxicity testing under Annex IX to EU REACH (ECHA, 2020e).

- The Environment Agency has not fully considered the mammalian toxicology information presented in the EU REACH registration (Section 8). However, the Registrant may wish to include additional information and more detailed RSS on the available testing for related substances to support the current data waiving. As above, it is recommended that this should consider the relevant ECHA guidance on grouping and read-across. Any additional references and regulatory information on the safety of PFiHx when used in medical devices or procedures could also be included.
- In the absence of scientifically justified arguments about the lack of ecotoxicity, it is recommended that a 'safety net' Aquatic Chronic 4 classification is applied under CLP (Section 9.1). This would trigger the production of a CSR with appropriate PNEC values and quantitative environmental exposure estimates, including substantiation for the statement of 'negligible emission to wastewater' at the manufacturing site (Section 10.1.2).
- If the UK supplier can demonstrate convincingly that PFiHx is not toxic to aquatic organisms, detailed information on its UK level of supply, use pattern and emissions to air from all stages of the life cycle should still be provided due to its high Global Warming Potential (GWP). This could include incorporation of PFiHx into monitoring programmes in relevant environmental media/compartments (Section 10).

PFiHx has a high Global Warming Potential. The UK supplier is invited to consider this as part of any voluntary action it may take to improve emission controls.

12.2.2 General regulatory recommendations for consideration by relevant UK authorities

The proposed EU PMT/vPvM criteria are not an official hazard category under UK REACH. Development of Government policy on PMT/vPvM criteria and the risk management implications for substances of this type could provide benefits to reduce potential risks posed to the environment and human health.

The Environment Agency along with HSE have been undertaking a Regulatory Management Options Analysis (RMOA) for PFAS, and the information summarised in this evaluation has fed into that analysis to identify the most appropriate risk management measures for PFAS in a UK context.

The implications for not listing PFiHx under the F-gas legislation could also be considered in a UK context.

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14 List of abbreviations

%	Percentage
B	Bioaccumulative
BCF	Bioconcentration factor
BMF	Biomagnification factor
bw	body weight
CAS	Chemical Abstracts Service
CLP	Classification, labelling and packaging (of substances and mixtures)
cm	Centimetre
CoRAP	Community Rolling Action Plan
CSR	Chemical Safety Report
d	Day
$DegT_{50}$	Degradation half-life or transformation half-life (days)
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
DSD	Dangerous Substances Directive
DT_{50}	Dissipation half-life (days)
dw	Dry weight
EC_{10}	10% effect concentration
EC_{50}	50% effect concentration
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EPM	Equilibrium Partitioning Method

EQS	Environmental Quality Standard
ERC	Environmental release category
ES	Exposure Scenario
EU	European Union
EUSES	European Union System for the Evaluation of Substances
g	Gramme
GC	Gas chromatography
GC/FID	Gas chromatography – Flame Ionisation Detection
GC/MS	Gas chromatography – mass spectrometry
GLP	Good laboratory practice
H	Hours
HLC	Henry's Law Constant
hPa	Hectopascal
HPLC	High performance liquid chromatography
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
kJ	Kilojoule
km	Kilometre
K_{AW}	Air-water partition coefficient
K_{OA}	Octanol-air partition coefficient
K_{OC}	Organic carbon-water partition coefficient
K_{OW}	Octanol-water partition coefficient
kPa	Kilopascal

$K_{SUSP–WATER}$	Suspended matter–water partitioning coefficient
k_X	Rate constants (days-1)
L	Litre
LC_{50}	50% lethal effect concentration
LOD	Limit of detection
Log	Logarithmic value
LOQ	Limit of quantitation
M	Molar
m/z	Mass to charge ratio
mg	Milligram
min	Minute
mL	Millilitre
mol	Mole
MS	Mass spectrometry
nm	Nanometre
NOAEL	No observed adverse effect level
NOEC	No-observed effect concentration
NOEL	No observed effect level
NONS	Notification of New Substances Regulations 1993
OC	Operational condition
OECD	Organisation for Economic Co-operation and Development
OSPAR	Oslo and Paris Convention for the Protection of the Marine Environment of the North-East Atlantic
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
p	Statistical probability

Pa	Pascal
PACT	Public Activities Co-ordination Tool
PBT	Persistent, Bioaccumulative and Toxic
PC	Product category
PEC	Predicted environmental concentration
pg	Picogramme
PFAS	Per- and polyfluorinated alkyl substances
PFC	Perfluorocarbon
PFCA	Perfluoroalkyl carboxylic acids
PFOS	Perfluorooctanesulfonate
pKa	Acid dissociation constant
PNEC	Predicted no effect concentration
POP	Persistent organic pollutant
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
PROC	Process Category
QSAR	Quantitative structure-activity relationship
OPERA	OPEn structure–activity/property Relationship App
r^2	Correlation coefficient
RAAF	Read-Across Assessment Framework
RCR	Risk characterisation ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (EU Regulation No. 1907/2006)
RMM	Risk Management Measures
RPE	Respiratory protective equipment

rpm	Revolutions per minute
SMILES	Simplified Molecular Input Line Entry System
SVHC	Substance of Very High Concern
t	Tonne
T.E.S.T.	Toxicity Estimation Software Tool
TG	Test Guideline
TSCA	Toxic Substances Control Act
UK	United Kingdom
US EPA	United Stated Environmental Protection Agency
UV	Ultraviolet
vB	Very bioaccumulative
vP	Very persistent
VP	Vapour pressure
vPvB	Very persistent and very bioaccumulative
WAF	Water Accommodated Fraction
WSF	Water Soluble Fraction
wt	Weight
w/v	Weight per volume
w/w	Weight per weight
ww	Wet weight
WWTP	Wastewater Treatment Plant
µg	Microgram

Appendix A: Literature search

A literature search was undertaken by the Environment Agency on 20th April 2020 to identify published information relevant to the assessment of PFiHx. The keywords listed in Table A.1 were searched for in PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Science Direct (https://www.sciencedirect.com/). In order to maximise the number of records identified keywords were based on the substance name only, and not on the endpoints of interest or year of publication.

Table A.1 Literature search terms and number of hits

Search terms	PubMed	Science Direct
355-04-4	0	16
1,1,1,2,2,3,3,4,5,5,5-Undecafluoro-4-(trifluoromethyl)pentane	0	0
Perfluoro(2-trifluoromethylpentane)	0	1
Perfluoroisohexane	0	2
Total unique records	**0**	**19**

The identified records were screened manually for relevance to this assessment based on the title and abstract. Articles identified as of potential interest were obtained and reviewed for relevance. Those that were found to be relevant are discussed in the appropriate sections of this report.

Appendix B: QSAR models

Two main databases were used to source *in silico* data for this evaluation when required. These were the United States Environmental Protection Agency (US EPA) CompTox Dashboard (US EPA, 2020a) and the Royal Society of Chemistry (RSC) ChemSpider portal (RSC, 2020a). Both integrate diverse types of relevant domain data through a cheminformatics platform and are built upon a database of curated substance properties linked to chemical structures (Williams *et al*., 2016).

The QSAR models available from these two platforms are presented in Table C.1 (data from other open access models are available in the CompTox dashboard, but for the sake of brevity, these have not been used for the purposes of this evaluation).

Table B.1 QSAR model outline

Name	Brief description
ACD/Labs	Predicts physicochemical properties via the Percepta Platform (http://www.acdlabs.com/products/percepta/).
EPISuite™ Estimation Programs Interface Suite™ for Microsoft® Windows	A Windows®-based suite of physical/chemical, environmental fate and ecotoxicity property estimation programs developed by the US EPA and Syracuse Research Corp. It uses a single input (typically a SMILES string) to run the following estimation programs: AOPWIN™, AEROWIN™, BCFBAF™, BioHCwin, BIOWIN™, ECOSAR™, HENRYWIN™, HYDROWIN™, KOAWIN™, KOCWIN™, KOWWIN™, LEV3EPI™, MPBPWIN™, STPWIN™, WATERNT™, WSKOWWIN™ and WVOLWIN™.
OPEn structure–activity/property Relationship App (OPERA)	Open source suite of QSAR models providing predictions and additional information including applicability domain and accuracy assessment, as described in Williams *et al.* (2016). All models were built on curated data and standardized chemical structures as described in Williams *et al.* (2017). All OPERA properties are predicted under ambient conditions of 760 mmHg (103 kPa) at 25 °C.
T.E.S.T. Toxicity Estimation Software Tool	US EPA software application for estimating the toxicity of chemicals using QSAR methods. EPISuite™ is the model used to generate some physico-chemical data, although T.E.S.T. does not report KOW values and uses a different database for surface tension. (US EPA, 2016).

EPISuite^{TM}

Table B.2 summarises the PFCs identified in the training / validation sets for EPISuite^{TM}. Applicability domain (US EPA, 2020c).

Table B.2 EPISuite^{TM} PFCs included in training and validation sets

EPISuite model	Training set	Validation set
MPBPVP v1.42	tetrafluoromethane hexafluoroethane tetrafluoroethylene octafluoropropane hexafluoropropene decafluorobutane perfluorocyclobutane perfluoro-n-hexane perfluorocyclohexane perfluoroheptane perfluoromethylcyclohexane	Not available
WSKOWWIN v 1.41	None identified	octafluoropropane octafluorocyclobutane
Water solubility estimate from fragments (v 1.01 est)	trifluoromethane	tetrafluoromethane hexafluoroethane octafluoropropane perfluorocyclobutane tetrafluoroethylene
KOAWIN v 1.1	Uses KOWWIN and HENRYWIN databases	
KOCWIN v 1.66	None identified	None identified
KOWWIN v 1.67	tetrafluoromethane hexafluoroethane	Perfluorocyclohexane
HENRYWIN v 3.1	tetrafluoromethane hexafluoroethane tetrafluoroethene	octafluoropropane perfluorocyclobutane

Open Structure-activity/property Relationship App (OPERA)

OPERA is a free and open-source/open-data suite of QSAR models providing predictions for physicochemical properties, environmental fate parameters, and toxicity endpoints. Applicability domain (AD) (Williams *et al.,* 2017):

- If a chemical is considered outside the global AD and has a low local AD index (< 0.4), the prediction can be unreliable.
- If a chemical is considered outside the global AD but the local AD index is average (0.4 - 0.6), the query chemical is on the boundary of the training set but has quite similar neighbours (average reliability). If the local AD index is high (> 0.6), the prediction can be trusted.
- If a chemical is considered inside the global AD but the local AD index is average (0.4 - 0.6), the query chemical falls in a “gap” of the chemical space of the model but

still falls within the boundaries of the training set and is surrounded with training chemicals. The prediction therefore should be considered with caution.

- If a chemical is considered inside the global AD and has a high local AD index (> 0.6), the prediction can be considered reliable.

T.E.S.T. (Toxicity Estimation Software Tool) (https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test)

Data sets used in T.E.S.T. (US EPA, 2016) for parameters reported at 25°C:

- Surface tension: Dataset for 1 416 chemicals obtained from the data compilation of Jasper 1972;
- Water solubility: Dataset of 5 020 chemicals was compiled from the database in EPI Suite^{TM}. Chemicals with water solubilities exceeding 1,000,000 mg/L were omitted from the overall dataset;
- Vapour pressure: Dataset of 2 511 chemicals was compiled from the database in EPI Suite^{TM}.

T.E.S.T. displays structures for substances from the test and training sets that are closest to the substance where a predicted value is required. A comparison between the experimental and predicted value for the substances in the test and training sets provides a similarity coefficient. If the predicted values match the experimental values for similar chemicals in the test and training set (and the similar chemicals were predicted well), there is greater confidence in the predicted value for the substance under evaluation.

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