SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Hexafluoropropene

EC No 204-127-4

CAS No 116-15-4

Evaluating Member State: Italy

Dated: 29 September 2020

Evaluating Member State Competent Authority

MSCA Italy
National Institute of Health on behalf of Ministry of Health
Viale Regina Elena, 299 - 00161 Rome, Italy.
In cooperation with Italian National Institute for Environmental Protection and Research (ISPRA).
Via Brancati, 48 - 00144 Rome, Italy

Tel.: +390649902061
FAX: +390649902286
Email: leonello.attias@iss.it

Year of evaluation in CoRAP: 2015

Before concluding the substance evaluation a Decision to request further information was issued on: 7 July 2017.

Further information on registered substances here:

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

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

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

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

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

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

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Hexafluoropropene (HFP) was originally selected for substance evaluation in order to clarify concerns about:

- suspected C
- suspected R
- high (aggregated) tonnage

During the evaluation also other concern was identified. The additional concern was:

- genotoxicity (suspected M)

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Compliance Check decision (Decision number: CCH-D-2114350400-66-01F).

Information available here: Dossier evaluations status

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State (eMSCA) to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

4. FOLLOW-UP AT EU LEVEL

4.1.1. Harmonised Classification and Labelling

Not applicable.

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

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

On the basis of the available information, a harmonized classification and labelling of the Substance for the following hazards: STOT SE 2 (H351: May cause damage to kidneys if inhaled) and Carc. 2 (H351) could be performed.

However, the Substance is used only as an intermediate, with no professional and consumer uses and exposure. Therefore, the eMSCA considers that the self-classification is sufficient to regulate the safe use for industrial workers.

5.2. Other actions

Not applicable.

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

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Hexafluoropropene (HFP) was originally selected for substance evaluation in order to clarify concerns about:

- suspected C
- suspected R
- high (aggregated) tonnage

During the evaluation also other concern was identified. The additional concern was:

- genotoxicity (suspected M)

Table 2

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Mutagenicity and carcinogenicity	The eMSCA used a stepwise approach in order to clarify the concern for mutagenicity and afterwards the concern for carcinogenicity. In the first SEv decision an *in vitro* mammalian cell micronucleus test with fluorescence *in situ* hybridization (FISH) or immunochemical labelling of kinetochores (CREST) (OECD 487 /EU B.49) was requested. The negative results reported in this assay together with the results of the already available genotoxicity studies allow to exclude a genotoxic MoA for carcinogenicity. The effects observed in the kidney in the 90-day study in mice and the assessement with the OECD (Q)SAR Toolbox suggest a possible nongenotoxic carcinogenicity similarly to Trichloro (or fluoro) ethylene and Tetrachloro (or fluoro) ethylene. Based on the similarity with other halogenated substances the Registrant(s) self-classify HFP as Carc. 2. HFP is an intermediate in the manufacturing processes, and it has no end use or professional or consumer uses. Moreover, the industrial uses are under strictly controlled conditions therefore the RMM in site are sufficiently protective from carcinogenicity hazard. Therefore, other requests for these endpoints are not justified under SEv.
Toxicity to reproduction	The available set of studies requested under CCH and performed by inhalation (extended one generation study in rats – OECD TG 443; prenatal developmrental toxicity study in rats and rabbits – OECD TG 414) is adequate and indicates that the Substance does not cause any effect on reproduction or development, besides those secondary to systemic /maternal toxicity. The eMSCA concludes that no classification is warranted.
Acute toxicity	The available acute toxicity study in rats via inhalation route, shows effects in the kidney after single exposure. The eMSCA is of the opinion that Specific Target Organ Toxicity – Single Exposure Category 2 (May cause damage to kidneys if inhaled) under EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008 could be envisaged. However, the Substance is used only as an intermediate, with no professional and consumer exposure.

	Therefore, the self-classification is considered sufficient by the eMSCA to regulate the safe use for industrial workers.

7.2. Procedure

The Substance evaluation of the Hexafluoropropene has started in March 2015.

The initial concerns were: suspected C; suspected R; high (aggregated) tonnage. In addition to the initial concerns, the eMSCA identified a concern for genotoxicity (suspected M). The eMSCA considered also the environmental aspects, but no additional concerns were raised.

The eMSCA considered that further information was required to clarify the concerns for mutagenicity and carcinogenicity. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 17 March 2016.

After discussion in the Member State Committee (MSC) meeting on 12-16 June 2017, a unanimous agreement of the MSC on the draft decision as modified at the meeting was reached. ECHA adopted the final decision on 7 July 2017 pursuant to Article 51(6) of the REACH Regulation.
During the evaluation period eMSCA had interaction with the Registrant(s).
The Registrant(s) updated the registration dossier on 12 October 2018 with the information requested in the SEv decision.

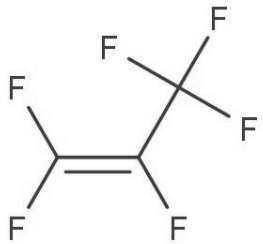
7.3. Identity of the substance

Table 3

SUBSTANCE IDENTITY	
Public name:	Hexafluoropropene
EC number:	204-127-4
CAS number:	116-15-4
Index number in Annex VI of the CLP Regulation:	602-061-00-4
Molecular formula:	C3F6
Molecular weight:	150.023 g/mol
Synonyms:	Hexalfuoroprop-1-ene

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 4

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	gaseous
Vapour pressure	587952 Pa at 25°C
Water solubility	82 mg/L at 28°C
Partition coefficient n-octanol/water (Log Kow)	1.95 at pH 7 and 20°C
Flammability	Non flammable. The test substance does not form flammable mixtures with air at atmospheric pressure and ambient temperature
Explosive properties	Data waiving
Oxidising properties	Data waiving
Stability in organic solvents and identity of relevant degradation products	Data waiving
Dissociation constant	Data waiving

7.5. Manufacture and uses

7.5.1. Quantities

Table 5

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☒ 10,000-50,000 t
☒ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

This substance is manufactured and/or imported in the European Economic Area in 10 000 - 100 000 tonnes per year.

Table 6

USES	
	Use(s)
Uses as intermediate	See below

Formulation	---
Uses at industrial sites	Used in the following products: polymers. Industrial use resulting in manufacture of another substance (use of intermediates). Used for the manufacture of: plastic products, chemicals and rubber products. Release to the environment of this substance can occur from industrial use: for thermoplastic manufacture and as an intermediate step in further manufacturing of another substance (use of intermediates).
Uses by professional workers	--
Consumer Uses	--
Article service life	--

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 7

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
602-061-00-4	hexafluoropropene	204-127-4	116-15-4	Press.Gas			
				Acute Tox. 4*	H332		
				STOT SE 3	H335		

7.6.2. Self-classification

- In the registration(s):

Liq. Gas H280
Acute Tox. 4 H332
Carc 2 H351
STOT SE 3 H335 Inhalation
STOT SE 2 H371 (Kidneys, Inhalation)
STOT RE 2 H373 (Kidneys, Inhalation)

- The following hazard classes are in addition notified in the C&L Inventory:

Press.Gas H280
STOT SE 2 H371 (Damage to organs)

STOT RE 2	H373 (Damage to organs)
Aquatic Chronic 3	H412

7.7. Environmental fate properties

7.7.1. Degradation

The eMSCA evaluated this endpoint and did not identify any concerns.

7.7.2. Environmental distribution

The eMSCA evaluated this endpoint and did not identify any concerns.

7.7.3. Bioaccumulation

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8.1.2. Aquatic invertebrates

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8.1.3. Algae and aquatic plants

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8.1.4. Sediment organisms

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8.1.5. Other aquatic organisms

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8.2. Terrestrial compartment

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8.3. Microbiological activity in sewage treatment systems

The eMSCA evaluated this endpoint and did not identify any concerns.

7.8.4. PNEC derivation and other hazard conclusions

Table 8

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the	**Hazard conclusion**	**Remarks/Justification**

environment compartment		
Freshwater	PNEC : 0.033 mg/L	Assessment factor : 1000. Lowest QSAR acute endpoint (algae EC50).
Marine water	PNEC: 0.003 mg/L	Assessment factor: 10000 Lowest QSAR acute endpoint (algae EC50).
Intermittent releases to water	PNEC:0.334 mg/L	Assessment factor: 100 Lowest QSAR acute endpoint (algae EC50).
Sediments (freshwater)	PNEC:0.279 mg/Kg dw	Equilibrium Partitioning Method (EPM) utilising PNECwater
Sediments (marine water)	PNEC:0.028 mg/Kg dw	Equilibrium Partitioning Method (EPM) utilising PNECwater
Sewage treatment plant	No derived	Based on a logKow<3 and limited potential for exposure and bioaccumulation and not considered necessary to derive a PNEC STP.
Soil	PNEC:0.264 mg/kg dw	Assessment factor: 1000. Using (Q)SAR derived value of 14d LC_{50} of 264.1 mg/kg dw on earthworm
Air	No hazard identified	
Secondary poisoning	Not derived; No potential for bioaccumulation	Based on the fact that the substance is a gas with a log Kow<3 and limited potential for exposure and bioaccumulation, it was not considered necessary to derive a PNEC oral

The eMSCA can support the conclusions on environmental hazard assessment. The eMSCA has only minor annotations on values for $PNEC_{sediment}$ and $PNEC_{soil}$ as follows:

$PNEC_{sediment}$ values are reported in mg/kg dry weight, but according to ECHA Guidance IR & CSA, Chapter R.10, $PNEC_{sediment}$ should be referred to kg of wet sediment. According to ECHA Guidance IR & CSA, Chapter R.10, $PNEC_{soil}$ should be referred to kg of wet soil.

7.8.5. Conclusions for classification and labelling

The Registrant(s) declare that data are conclusive but not sufficient for environmental classifications.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Three studies are submitted by the Registrant(s) regarding the toxicokinetics. Taken as a whole the studies confirm that HFP may be systemically absorbed via the inhalation route. The results of the in vitro studies indicate that HFP is metabolized to two different GSH-conjugates in rat liver and kidney (S-hexafloropropyl-glutathione and S-pentafluoropropenyl-glutatione - HFPG and PFPG, respectively). The data collected in the cannulated rats (to collect the bile) also suggest that HFP metabolites formed in the liver and eliminated with bile are not translocated to the kidney and that the bioactivation in the kidneys by GSH-conjugation may be responsible for HFP-induced nephrotoxicity.

7.9.2. Acute toxicity and Corrosion/Irritation

For the acute toxicity oral and dermal route and for corrosion/irritation the Registrant(s) presented a data waiving (studies technically not feasible). The eMSCA supports this conclusion.

For the inhalation route, the Registrant(s) have provided studies in rats and guinea pigs. In the study in guinea pigs the 4-hour inhalation LC50 was found to be between 2000 ppm and 2600 ppm. HFP causes damage to the kidneys and central nervous system. There was also evidence of pulmonary injury, which appeared in guinea pigs as congestion and edema. The LC50 in the study in rats exposed for 4-hour was 3060 ppm (18776 mg/m3). Due to the extent and irreversible nature of the kidney effects (nephrosis) at exposures of 2870 ppm and higher concentrations, the substance is self-classified as Acute Tox. 4 (H332: Harmful if inhaled). Moreover, due to the effects via inhalation route in the kidneys after single exposure, the Registrant(s) have self-classified HFP for Specific Target Organ Toxicity – Single Exposure Category 2 (STOT SE 2; H371: May cause damage to kidneys if inhaled) under EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008. The eMSCA concludes that Acute Tox. 4 and STOT SE 2 classifications are warranted.

In the same inhalation study in rats, respiratory irritation-related effects (edema and congestion) were observed at concentrations of 1250 ppm and higher. This study could be the basis for the current self-classification for respiratory irritation (STOT SE 3). However, the eMSCA notes that the test substance used in the study was contaminated with perfluoroisobutylene (PFIB), which is a known respiratory irritant. In subsequent rat inhalation studies using test substance with controlled PFIB levels, no exposure concentration dependent respiratory irritation was observed. Therefore, the eMSCA considers that the classification for respiratory irritation after single exposure (STOT SE 3) is not warrated.

7.9.3. Sensitisation

As the substance is a gas and guideline testing for sensitisation is not feasible, the Registrant(s) have adapted the skin sensitisation endpoint (Data waiver: studies technically not feasible).

The eMSCA supports this and concludes that there is no need to provide studies on skin sensitisation.

7.9.4. Repeated dose toxicity

In the mice study, Crl: CD-1(ICR) BR mice were exposed to target concentrations of 0, 10, 50 or 150 ppm HFP for 6 hours/day, 5 days/week for a period of approximately 90 days (25 males and 25 females). Mean body weights and body weight gains were not affected by exposures to the test material in all tested groups. No differences in food consumption

were noted in male or female mice during the study. Elevated levels of water consumption were observed in mice exposed to 150 ppm; these differences were statistically significant for female mice. Blue skin colour of the abdomen were observed in male mice exposed to 50 or 150 ppm. Hematology conducted in mice showed no effects related to HFP exposures. Microscopic lesions were observed in the kidneys of mice exposed to 50 of 150 ppm. The kidney lesions included regeneration of the inner cortical tubules, cytomegaly of tubular epithelium, and tubular epithelial necrosis. The NOAEL for 90 days of repeated inhalation exposure to HFP in mice is 10 ppm. The no-effect level following 28 days of recovery is also 10 ppm. At recovery, cytomegaly and kidney nephropathy were present in male mice. In the second study, Crl: CDBR rats,5 groups each of 20 males and 20 females, were exposed to target concentrations of 0, 10, 50 or 150 ppm HFP for 6 hours/day, for a period of approximately 90 days. Low mean lymphocyte count was observed in males exposed to 150 ppm. This effect was not observed following 28 days of recovery. There was no hematology or pathology findings to support the single observation of reduced mean lymphocyte count as an adverse effect. Other non-adverse or non-biologically significant effects were observed in the 50 and 150 ppm exposure groups. These included increased levels of fluoride in the urine, increased urine volume, decreased urine osmolality and increased water consumption and elevated levels of serum sodium in the male groups exposed to 50 or 150 ppm.

Rats were less sensitive to the effects of HFP than mice. Based on the results of repeated inhalation studies, the substance is self-classified by the Registrant(s) as Specific Target Organ Toxicity Repeated Exposure Category 2 (STOT RE 2; Kidney) according to the EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008. The eMSCA supports this conclusion.

7.9.5. Mutagenicity

A potential concern for mutagenicity was raised by the eMSCA during the substance evaluation process. The genotoxic potential of the substance was assessed based on both *in vitro* and *in vivo* studies.

Genotoxicity *in vitro*

Negative results were obtained in the Ames test and in gene mutation assay in mammalian cells both in the presence and absence of metabolic activation. In a mammalian chromosome aberration study in CHO cells, positive results (with and without metabolic activation) were reported. However, the eMSCA notes that there was no adequate assessment of the cytotoxicity (only a cell cycle delay was reported) and therefore it cannot be excluded that the reported positive result was a result of cytotoxicity.

Genotoxicity *in vivo*

The Registrant(s) have provided one *in vivo* chromosome aberration test equivalent or similar to OECD 475 via inhalation in mouse. The result was weakly positive only in male mouse at the highest concentration (1200 ppm). The Registrant(s) consider that the data support a negative conclusion. The eMSCA considers the result as potentially false positive.

In vivo micronucleus study according to OECD 474 via inhalation in mouse was negative. An unscheduled DNA synthesis (UDS) study via inhalation in male rats with negative results and a dominant lethal mutation assay via inhaltion in rats with negative results have also been provided. UDS and dominant lethal assay are known to have a poor sensitivity and are currently used in risk assessment only to address very specific questions: the dominant lethal test can be used to verify the crossing of the gonadal barrier and the effects on germ cells; the UDS is able to detect only a narrow spectrum of DNA lesions able to trigger the nucleotide excision repair.

Overall the genotoxicity data set was considered inconclusive by the eMSCA. Therefore, a new *in vitro* micronucleus assay, performed according to the current OECD TG 487, in which the cytotoxity can be reliably monitored, was requested in the first SEv decision.

New *in vitro* micronucleus assay

A new *in vitro* micronucleus assay (OECD 487) performed in human lymphoblastoid TK6 cells was submitted by the Registrant in 2018. In this test, HFP did neither induce micronuclei during 4-hour incubations both, with or without metabolic activation nor in a 27-hour incubation without metabolic activation. Therefore, HPF is considered negative for the induction of clastogenicity and aneugenicity under the conditions of this test system.

Conclusion

The eMSCA concludes that HFP is considered not to be genotoxic. Therefore, no classification for mutagenicity is warranted.

7.9.6. Carcinogenicity

No carcinogenicity data are available for the substance.

The Registrant(s) documented that the substance is used in strictly controlled conditions at all life cycle stages, therefore according to the column 2 of Annex X Section 8.9.1 no carcinogenicity study is required.

The eMSCA considers that the concern for carcinogenicity of HFP is substantiated by the fact that there is evidence of carcinogenicity of substances sharing a common haloethylene structure (trichloroethylene; tetrachloroethylene; tetrafluoroethylene). Tetrafluoroethylene (CAS 116-14-3) has been self-classified as Carc. 1B. Ireland submitted a CLH proposal (24th of August 2018) as Carc. 1B with a non-genotoxic MoA for tetrafluoroethylene. RAC agreed with the proposal and the RAC opinion was adopted on 5th December 2019. Trichloroethylene (CAS 79-01-6) has a harmonized classification as Carc. 1B. Tetrachloroethylene (CAS 127-18-4) has a harmonized classification as Carc. 2, and a recent new evaluation performed by IARC (2014) defined the substance as carcinogen category 2A. Therefore, the eMSCA considers the possibility that a higher classification may be appropriate (possible equivalent to category 1B of CLP) for tetrachloroethylene. The Substance Evaluation of tetrachloroethylene, published in the 2014, reported no need for regulatory follow-up action.

In particular, the kidney is identified as a common target for tumour formation for trichloroethylene, tetrachloroethylene and tetrafluoroethylene. The proposed mode of action involves the glutathione conjugate that is further activated in the kidney by the β-lyase. Based on the findings in repeated dose toxicity studies, kidney is also a target organ for HFP.

Suspicion that HFP might be carcinogenic is limited to a potential kidney tumour formation by a non-genotoxic mechanism. Based on a weight-of-evidence approach using existing genotoxicity studies with HFP, there is no concern of a genotoxic mode of action for HFP. On this basis, the Registrant(s) self-classify the substance as Carc. 2.

Based on the available data the eMSCA could not exclude that HFP could act as tetrafluoroethylene in the induction of kidney tumours in the experimental animals. In fact, the kidney is the target organ of HFP toxicity. The Registrant(s), based on the toxicokinetic data, speculate that the conjugation of hexafluoropropene with glutathione (GSH) in the kidney may be an important step in the bioactivation of hexafluoropropene. S-hexafluoropropyl-glutathione (HFPG) formed in the kidney could be processed by gamma-glutamyltranspeptidase and dipeptidases to the corresponding cysteine S-conjugate, which is metabolized by renal cysteine conjugate b-lyase, to give an electrophilic intermediate, most likely a thionoacyl fluoride. The eMSCA considers that the kidney effects induced by

HFP are qualitatively similar to those produced by repeated inhalation exposure to tetrafluoroethylene (RAC considers that a harmonized classification as Carc. 1B is warranted; the RAC opinion was adopted on 5th December 2019).

Considering that HFP is used only at industrial site under strictly controlled conditions (no end uses or professional and consumer uses are reported) and it is self-classified as Carc. 2, the eMSCA is of the opinion that the Risk management measures in place are sufficiently protective for workers. The eMSCA considered a request of a new carcinogenicity study, aimed to verify the adeguacy of the current classification, not proportionate, and not in line with the aim of REACH to avoid unnecessary animal testing.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Two sets of studies are performed by the Registrant(s) to evaluate the toxicity to reproduction (effects on fertility and developmental toxicity).

1) An *Extended One-Generation study (OECD 443)* was performed: Wistar rats were exposed by inhalation (whole body, 6 hours/day: intended target concentrations: 0 ppm, 50 ppm, 300 ppm and 900 ppm) during a premating period of 10 weeks and during mating (up to 2 weeks), gestation and lactation until postnatal day 21. At weaning, pups were distributed to Cohorts 1A and 1B and were exposed to the test substance at lower concentrations as their parents up to adulthood (intended target concentrations: 0 ppm, 50 ppm, 300 ppm and 600 ppm). However, due to mortality and evident signs of distress observed in both P0 and F1 at the top concentrations target concentrations were lowered during exposure of the P0-generation (from 900 ppm to 600 ppm) and the target concentrations of the mid- and high-concentration groups of the F1-generation were lowered before the start (day 0) of Cohort 1A and Cohort 1B (from 300 ppm to 100 ppm and from 600 ppm to 200 ppm, respectively).

Body weights and food consumption were reduced at top dose (P0) and at the top- and mid-dose (F1). A number of dose-related changes in relative organ of weight, the most pronounced being the increase in kidney weight, were observed at top and mid-dose, occurred in both P0 and F1 and were considered as treatment-related adverse changes. Histopathology revelead nephropathy (top and mid-dose) and heart muscle degeneration (top dose of P0 only).

Conversely, no statistically or biologically significant changes were observed in the fertility parameters, litter parameters, oestrus cycle or thyroid hormone levels at any dose level. Also no treatment-related effects were observed on splenic lymphocyte subpopulation analysis in Cohort 1A animals of the F1-generation. The pup weight at weaning was significantly reduced at top and mid-dose; this effect was considered likely to be related to general toxicity.

In conclusion no effects that may trigger a classification for "toxic to reproduction" were observed. The LOAEL and NOAEL for systemic toxicity (adults, juvenile and neonatal animals) were 100 ppm and 50 ppm.

2) Two *developmental toxicity studies (OECD TG 414)* were performed by inhalation in Wistar rats (whole body, 6 hours/day: 0, 50, 300, 900 ppm on gestational days 6-20) and in NZW rabbits (whole body, 6 hours/day: 0, 10, 50, 300 ppm on gestational days 6-28)

- In the rat study the mid- and top dose caused a dose-related decrease of weight gain and feed intake in dams. An increase in weight of the kidneys was observed down to the low dose of 50 ppm. Macroscopic pathologic observation of the kidneys showed enlargement and discoloration in the 900 ppm group; however no histopathology was performed. Dose-related decrease in fetal weight and delayed skeletal ossification were observed at mid- and top-dose. No other changes were seen in the litters. The developmental LOAEL and NOAEL were 300 and 50 ppm.

Due to the presence of a significant increase in kidney weight, in the absence of an histopathological examination that could assess the adversity of the change, the level of 50 ppm is conservatively defined as a maternal LOAEL. The developmental effects in rats are a likely secondary consequence of maternal toxicity and do not warrant classification.

- In the rabbit study top dose caused a significant but transient decrease of weight gain and feed intake in dams. At the same dose level a delayed skeletal ossification was observed, which is a likely secondary consequence of maternal toxicity. No other changes were seen in the dams or litters. The maternal and developmental LOAEL and NOAEL were 300 and 50 ppm.

Conclusions

An adequate set of studies performed by inhalation (extended one generation in rats – OCED TG 443; prenatal developmrental toxicity in rats and rabbits – OECD TG 414) indicates that the substance does not cause any effect on reproduction or development, besides those secondary to systemic /maternal toxicity. The eMSCA concludes that no classification is warranted.

7.9.8. Hazard assessment of physico-chemical properties

Not relevant for this evaluation.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Table 9

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Workers Inhalation	Acute-systemic effects	Acute toxicity		DNEL: 46 mg/m^3	AF for dose response relationship: 1 AF for interspecies differences (allometric scaling): 1 AF for other interspecies differences: 2.5 AF for intraspecies differences: 5 AF for the quality of the whole database: 1 AF for remaining uncertainties: 1 Overall Assessment Factor: 12.5
Workers Inhalation	Long term-systemic effects	Repeated dose toxicity		DNEL: 0.62 mg/m^3	AF for dose response relationship: 1 AF for difference in duration of exposure: 2 AF for interspecies differences (allometric scaling): 1

					AF for other interspecies differences: 2.5 AF for intraspecies differences: 5 AF for the quality of the whole database: 2 Overall Assessment Factor: 50
General population Inhalation	Acute-systemic effects	Acute toxicity		DNEL: 34 mg/m^3	AF for dose response relationship: 1 AF for interspecies differences (allometric scaling): 1 AF for other interspecies differences: 2.5 AF for intraspecies differences: 10 AF for the quality of the whole database: 1 AF for remaining uncertainties: 1 Overall Assessment Factor: 25
General population Inhalation	Long term-systemic effects	Repeated dose toxicity		DNEL: 0.15 mg/m^3	AF for dose response relationship: 1 AF for difference in duration of exposure: 2 AF for interspecies differences (allometric scaling): 1 AF for other interspecies differences: 2.5 AF for intraspecies differences: 10 AF for the quality of the whole database: 2 Overall Assessment Factor: 100

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

On the basis of the available information, a harmonized classification of the substance could be envisaged by the eMSCA, for the following hazards: STOT SE 2 (H351: May cause damage to kidneys if inhaled) and Carc. 2 (H351).

However, the substance used only as an intermediate, with no professional and consumer uses or exposure, the self-classification is considered sufficient by the eMSCA to regulate the safe use for industrial workers.

7.10. Assessment of endocrine disrupting (ED) properties

Not relevant for this evaluation.

7.11. PBT and VPVB assessment

Given all available data on biotic and abiotic degradation, bioaccumulation and toxicity, the eMSCA concludes that this substance does not fulfil the PBT criteria (not PBT) nor does it fulfil the vPvB criteria (not vPvB).

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

In the CSR the Registrant(s) report that since the Substance is a gas and inhalation would be the main route of exposure for the minimal exposure that might occur, dermal exposure is not relevant due to the fast rate of evaporation. The ECETOC TRA model and measured worker exposure data have been used in the life cycle exposure assessment. This approach demonstrates that there is a minimal risk for exposure. Any release to the environment is expected to partition to the air. The manufacturing process is reported to be a strictly controlled in a closed system that is operated with strict controls so there is only little potential for exposure. The eMSCA is of the opinion that the justification for the very low worker exposure given by the registrant is appropriate.

7.12.1.2. Consumer

Not relevant: HFP is not used by consumers.

7.12.2. Environment

In the CSR, the Registrant(s) state that the ECETOC TRAM 1.1 (released May 2010) was used for the environmental assessment. The EUSES model was also run to confirm that the ECETOC TRAM 1.1 gave equivalent exposure estimates compared to EUSES.

The Registrant(s) report the distribution modelling calculation according to Mackay, Level III. The reported data show that the substance will distribute primarily to air. The Registrant(s) explain that under environmentally relevant conditions, the test substance is a gas. Moreover Registrant(s) highlight that due to high volatility, test substance would readily volatilize into the atmosphere from soil.

The environmental exposure assessment is completely driven by the annual reported HFP emissions to air. The results are linear with respect to air emissions. In the CSR, the Registrant(s) also report that the environmental exposure is performed once with all uses combined at one site for a worst case scenario.

The eMSCA has assessed all PECs estimation for each compartment as well as ECETOC TRAM 1.1 input data, operational conditions (OC) and risk management measures (RMM) as reported by the Registrant(s). The eMSCA can support the results for environmental exposure assessment indicating negligible exposure to HFP based on the uses identified.

7.12.2.1. Aquatic compartment (incl. sediment)

The Registrant(s) declare that there are no releases to aquatic compartments. The eMSCA can support this conclusion.

7.12.2.2. Terrestrial compartment

The Registrant(s) declare that there are no releases to terrestrial compartment. Furthermore, the Registrant(s) highlight that HFP is a volatile gas that is unlikely to stay in the soil and progress up the food chain. The eMSCA can support this conclusion.

7.12.2.3. Atmospheric compartment

The Registrant(s) declare that the environmental exposure is completely driven by the annual HFP emissions to air. Furthermore, the Registrant(s) highlight that emissions to the air for each site and use depend more on the capture efficiencies of pollution control than on the tonnage used.

The eMSCA noted that the consortia members reported their air emissions per site which they must record and report to the authorities. The eMSCA can support these conclusions.

7.12.3. Combined exposure assessment

In the CSR, the Registrant(s) declare that the environmental exposure is performed once with all uses combined at one site for a worst case scenario." The eMSCA can support this.

7.13. Risk characterisation

Based on the risk characterization ratios reported by the Registrant(s), there are no significant exposures to HFP based on the uses identified. The eMSCA agrees that all reported RCRs are indicating safe use and negligible exposure.

7.14. References

Registration dossier for Hexafluoropropene, European Chemicals Agency.

7.15. Abbreviations

AF Assessment factor
BW Body weight
CAS Chemical abstracts service
C&L Classification and labelling
CLP Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR Carcinogenicity, mutagenicity and toxicity to reproduction
CSR Chemical Safety Report
DMEL Derived Minimal Effect Level
DNEL Derived no effect level
ES Exposure Scenario
eMSCA Evaluating Member State Competent Authority
NOAEC No Observed Adverse Effect Concentration
NOAEL No Observed Adverse Effect Level
NOEC No Observed Effect Concentration
LOAEL Lowest-Observed-Adverse-Effect Level
LOAEC Lowest-Observed-Adverse-Effect Concentration
OECD Organisation for Economic Co-operation and Development
PBT Persistent, Bioaccumulative, Toxic
PEC Predicted Environmental Concentration
PNEC Predicted No Effect Concentration
RCR Risk characterization ratio
RMMs Risk Management Measures
vPvB Very Persistent and very Bioaccumulative