EUROPEAN CHEMICALS AGENCY

Helsinki, 15 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114350400-66-01/F
Substance name: Hexafluoropropene
EC number: 204-127-4
CAS number: 116-15-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 01.07.2016
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), inhalation route with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), inhalation route with the registered substance;**

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3; test method: OECD TG 443) in rats, inhalation route with the registered substance;**

   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **24 June 2019**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have sought to adapt this information requirement according to Annex XI, Section 3. You provided the following justification for the adaptation *"In accordance with Section 3 of REACH Annex XI, Substance-tailored exposure driven testing, this test, information requirement 8.7.2 in accordance with (Annex IX and X) may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report".*

The adaptation should meet the general rule for adaptation of Annex XI Section 3.2 where you need to specifically demonstrate that the conditions of sections (a), (b) or (c), as appropriate, are fulfilled. In your dossier you have not clearly specified which particular rule you invoke, but it is understood that the adaptation is claimed under Annex XI Section 3.2 (c), as based on the information in your dossier neither adaptation of Annex XI Section 3.2. (a) nor (b) could apply. In particular, Annex XI section 3.2.(a) is not appropriate as a means to seek to omit the testing, as you have not provided a DNEL for developmental effects and as such for this endpoint it is not possible to verify the significance of the exposures you have predicted in the exposure scenarios for developmental effects. Further it appears you do not fully preclude the possibility of incorporation within an article and as such Annex XI Section 3.2.(b) is not appropriate, as exposure due incorporation within articles is not excluded.

ECHA also notes that your adaptation does not meet the requirements of Annex XI 3.2(c) where the substance is potentially incorporated in an article.

ECHA notes that your adaptation does not meet Annex XI section 3.2.(c) (i) where you indicate that *"The predicted quantitative exposure to the bound monomer for workers, consumers and the environment would be extremely low".* ECHA understands that you seek to demonstrate the substance is not released during its life cycle from an article made of polymeric material. ECHA notes that you have not provided any evidence other than to assert *"HFP is a residual and was estimated to be less than 0.001% of the polymer".* It is not stated what polymer products are available and what would need to be assessed to ensure no release during the life cycle.
There is no support to your assertion through provision of some analytical evidence, such as reported levels of HFP within a polymer product or evidence of absence from a headspace analysis above a sample of the polymer under reasonably worst case conditions and using a sensitive analytical method. Currently you provide no such evidence that the substance is not released during its life cycle.

Annex XI 3.2.(c)(ii) requires you to demonstrate that the likelihood that workers or the general public or the environment are exposed to the substance under normal or reasonably foreseeable conditons of use is negligible. You have not been able to demonstrate the above. In fact, you provide evidence that worker exposure is possible. Exposure to the general public cannot be determined for the reasons provided in the paragraph above.

Annex XI 3.2.(c)(iii) requires you to clearly demonstrate that throughout the life cycle (or during all manufacturing and production stages) stricly controlled conditions as set out in Article 18(4)(a)-(f) apply. You have described the industrial process with respect to ES1 and ES2 and provided some assertion that strictly controlled conditions are fulfilled as set out in Article 18(4)(a)-(f). However, you have estimated exposure levels by using exposure modelling that undermines the limited qualitative assurance provided in the CSR. For example, for ES1, inhalation exposure is estimated at [redacted] mg/m^3, and for ES2 [redacted] mg/m^3. These exposure estimations do not in themselves support the strictly controlled conditions that would be required to support an exposure based adaptation in line with Annex XI 3.2.(c)(iii) of the REACH regulation – they are generic modelled exposures and no further evidence demonstrating the routine absence of exposure and the details of plant to ensure rigorous containment is provided in the dossier. There are no measured data, showing absence of exposure using a sensitive method. In the current CSR you describe warning alarms that are set at levels of about [redacted]% of the DNEL, which is not an insignificant release level in the context of rigorous containment. Alarms set at [redacted]% of the DNEL you have derived in itself does not preclude the possibility of personal exposures.

Because of the deficiencies highlighted above, ECHA considers that the adaptation of the information requirement you have provided does not currently meet any of the conditions set in Annex XI, section 3, and therefore is rejected.

Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the inhalation route is the most appropriate route of administration for gaseous substances as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a gas, ECHA concludes that testing should be performed by the inhalation route.

In your dossier and comments on the draft decision you sought to adapt the information requirements for reproductive and developmental endpoints with a variety of arguments. You refer to a study record for a sub-chronic 90-day inhalation toxicity study. ECHA notes that, this study does not provide the information required by Annex X, Section 8.7.3. because it is not a reproduction toxicity study and does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. You also refer to reproductive endpoints evaluated in a dominant lethal test (according to EPA OPPTS 870.5450, Rodent Dominant Lethal Assay, 1988) performed in male rats.

ECHA notes, that even if this test provides useful information it does not provide the necessary information required from a prenatal developmental toxicity study.

In addition, ECHA considers that a "sentinel effect of kidney toxicity" is not a valid adaptation according to column 2 of Annexes IX and X, Sections 8.7.2 and 8.7.3., or according to the general rules of Annex XI.

ECHA furthermore considers that your "computational toxicology assessment", using ADMET Predictor and TOPKAT, is documented poorly that ECHA is unable to establish the methodology for what you have done. ECHA notes that the requirement of Annex XI, 1.3, for adequate and reliable documentation of the applied method, is not met.

You have proposed that the DNEL and TLV of 0.1 ppm is protective of worker safety. ECHA considers this to be an adaptation according to Annex XI, 3.2(a). ECHA notes that footnote (1) of Annex XI, 3.2(a)(ii) is not satisfied, and so it is not possible to establish that a DNEL can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes.

In your formal comments you also provided extensive information on the means by which you seek to control the substance in the workplace.

You provided a detailed description of your procedures in the manufacturing phase and during polymerization of HFP. The documentation seeks to fulfill the description of strictly controlled conditions according to Art 18 (4) a-f. You cite procedures for controlling leaks and restricting exposure at manufacturing sites e.g. alarm systems, control rooms for workers, monitoring programmes, guidance for accidents and special situations. You also provide information of the residues and releases of monomer in polymer.

The documentation appears to fulfil the description of Art 18 (4) a-f, with one exception. Current monitoring data in the received comments are rather limited though you indicate you plan further monitoring of workers. A long-term (6-hour) personal monitoring result of [redacted]% of the DNEL (as you have reported) is unlikely to be considered indicative of the standard required for strictly controlled conditions. If your intended adaptation is to be successful, it is important for you, along with descriptions of engineering controls and procedures, to demonstrate where possible routine absence of exposure and minimisation of emissions. Additionally, there appear to be some inconsistencies in the limit of detection for the methods quoted in your methodology (2 ppb) and those reported in the exposure assessment (approx. 10 ppb).
This information is not included in the IUCLID dossier at the moment, and therefore, though relevant to the case, does not allow the information requirement to be adapted as the dossier cannot be considered compliant at this stage of the decision-making process.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the inhalation route.

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2. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier does not contain information on a pre-natal developmental toxicity study with the registered substance.

You have sought to adapt this information requirement according to Annex XI, Section 3. You provided the following justification for the adaptation *"In accordance with Section 3 of REACH Annex XI, Substance-tailored exposure driven testing, this test, information requirement 8.7.2 in accordance with (Annex IX and X) may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report".*
The adaptation should meet the general rule for adaptation of Annex XI Section 3.2 where you need to specifically demonstrate that the conditions of sections (a), (b) or (c) as appropriate are fulfilled. Because of the deficiencies highlighted in the section 1. above, ECHA considers that the adaptation of the information requirement you have provided does not currently meet any of the conditions set in Annex XI, section 3, and therefore is rejected.

Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

ECHA considers that the inhalation route is the most appropriate route of administration for gaseous substances as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a gas, ECHA concludes that testing should be performed by the inhalation route.

In your dossier and comments on the draft decision you sought to adapt the information requirements for reproductive and developmental endpoints by using several arguments. You also provided extensive information on the means by which you seek to control the substance in the workplace. As explained in more detail in Section 1. above, ECHA considers that the adaptations of the information requirement you have provided do not currently meet any of the conditions set column 2 of Annexes IX and X, Sections 8.7.2 and 8.7.3. or with the general rules of Annex XI for this standard information requirement and are therefore rejected.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit or rat) by the inhalation route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

3. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.3. or with the general rules of Annex XI for this standard information requirement.

In the technical dossier you have provided a study record for a sub-chronic 90-day inhalation toxicity study (USEPA Fluoralkenes Final Test Rule) for the EOGRTS endpoint. However, this study does not provide the information required by Annex X, Section 8.7.3. because it is not a reproduction toxicity study and does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study.

More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, mating, pregnancy and lactation phases, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.
Therefore, your adaptation of the information requirement is rejected.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the inhalation route is the most appropriate route of administration for gaseous substances as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a gas, ECHA concludes that testing should be performed by the inhalation route.

In your dossier and comments on the draft decision you sought to adapt the information requirements for reproductive and developmental endpoints by using several arguments. You also provided extensive information on the means by which you seek to control the substance in the workplace.

As explained in more detail in Section 1. above, ECHA considers that the adaptations of the information requirement you have provided do not currently meet any of the conditions set column 2 of Annexes IX and X, Sections 8.7.2 and 8.7.3. or with the general rules of Annex XI for this standard information requirement and are therefore rejected.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, inhalation route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity)] were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 22 June 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2015. The Substance Evaluation process is currently ongoing as of July 2016. The information from this compliance check may be further considered in the ongoing Substance Evaluation process.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

3. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.