~~Confidential~~

Helsinki, 02 December 2021

Addressees
Registrants of JS_436-710-6 listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
09/02/2021

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1,1,1,2,2,4,5,5,5-nonafluoro-4-(trifluoromethyl)-3-pentanone
EC number: 436-710-6

Decision number: Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)

DECISION ON TESTING PROPOSAL(S)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by **8 September 2025**.

The requested information must be generated using the Substance unless otherwise specified.

A. Information required from the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) by inhalation route, in a second species (rabbit)

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) by inhalation route, in rats, specified as follows:

   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic 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; and
   - Cohort 3 (Developmental immunotoxicity).

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annex X of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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, has to 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.

Approved[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

[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 A: Reasons to request information required under Annex X of REACH

This decision is based on the examination of the testing proposals you submitted.

1. Pre-natal developmental toxicity study in a second species

A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in two species is a standard information requirement under Annex X, Section 8.7.2. to REACH.

1.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for a PNDT study according to OECD TG 414 with the Substance.

In your registration dossier, you provide information on a PNDT study conducted with rat as a first species ([redacted] 2012), but there is no study record on a study in a second species.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Developmental toxicity. You provided your considerations concluding that there were no Column 2 waivers for this endpoint at Annex X which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

Within the alternative methods considerations you request that the performance of a second PNDT study '*only be required if ECHA deems that it is scientifically necessary considering the weight of evidence already available addressing the lack reprodutive and developmental effects of the test article'.* ECHA notes that you refer to OECD TG 421, 414 and 413 studies with the Substance (all conducted in rats) in your considerations, however you have not provided any documentation or further justification for this weight of evidence approach to fulfil the information requirement for pre-natal developmental toxicity in two species. Therefore, ECHA cannot assess it.

You further propose to conduct this PNDT study in a second species only after receiving the results of the Extended one-generation reproductive toxicity (EOGRT) study that is also being proposed (request A.2. of this decision). ECHA notes that the timeline allows for sequential testing.

ECHA agrees that a PNDT study in a second species is necessary.

1.2. Specification of the study design

You proposed testing in the rabbit as a second species. The study in the first species was conducted in the rat. The rat or the rabbit are the preferred species under the OECD TG 414 (ECHA Guidance R.7a, Section R.7.6.2.3.2.). Therefore, the study must be conducted in the rabbit.

You proposed testing by inhalation route. ECHA agrees with your proposal.

1.3. Outcome

Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test with the Substance, as specified above.
In your comments on the proposed amendment, you agree with this request.

2. Extended one-generation reproductive toxicity study

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

2.1 Information provided to fulfil the information requirement

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the Substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Toxicity to reproduction. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA agrees that an EOGRTS is necessary.

2.2 Specification of the study design

Species and route selection

You proposed testing in the rat. ECHA agrees with your proposal because the rat is the species preferred by OECD TG 443.

You proposed testing by inhalation route. ECHA agrees with your proposal.

Pre-mating exposure duration and dose-level setting

You proposed two weeks pre-mating exposure duration. ECHA disagrees with your proposal. Ten weeks pre-mating exposure duration is required because there is no substance specific information in the dossier supporting shorter pre-mating exposure duration (ECHA Guidance R.7a, Appendix R.7.6-3).

You propose that the *'Dose levels will be selected based on the results from the OECD 421 and OECD 414 studies that were already been conducted on the test article.'* ECHA agrees that all available information should be taken into account.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level must aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects, with the other cohorts being tested at the same dose levels. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study.

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

In your comments on the proposed amendment, you agree with the ten week pre-mating exposure duration. Furthermore, you agree with the dose level selection, and indicate your

intention to conduct a dose range finding study prior to initiation of the main OECD TG 443 study.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and shall be included.

Cohort 3

You have proposed not to include Cohort 3. However, ECHA considers that the criteria to include Cohort 3 are met for the following reasons.

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

Existing information on substance(s) structurally analogous to the Substance show evidence of immunotoxicity as explained below. This raises a particular concern on (developmental) immunotoxicity also for the Substance.

There is structural similarity between the Substance (C6 perfluorinated ketone) and other per- and polyfluoroalkyl substances (PFAS), such as HFPO-DA (Hexafluoropropylene oxide dimer acid; C6 perfluorinated carboxylic ether acid), PFOA (Perfluorooctanoic acid; C8 perfluorinated carboxylic acid) and PFOS (Perfluorooctane-1-sulphonic acid; C8 perfluorinated sulphonic acid). Although the Substance does not contain an acid group, it is structurally similar to other members of the PFAS group because the overall size of the molecules' carbon chain is similar and the carbon backbone chains are heavily fluorinated.

There is a similar toxicity profile between the Substance and the structurally similar PFAS. The effects observed for the Substance in the available OECD TG 412 study (e.g. increased liver weight, induction of peroxisome proliferation, disturbances in lipid metabolism) are typical also for other PFAS (EFSA, 2020[2]; SVHC support document, 2019[3]; Rushing, 2017[4]).

PFAS are known to cause immunotoxicity. For example, PFOS has been shown to cause changes in weights of lymphoid organs (thymus, spleen) and cellularity of these organs (e.g. induction of apoptosis in splenocytes and thymocytes) (EFSA, 2020[2]). For HFPO-DA, reduced spleen weights have been reported (Rushing, 2017[4]). Also for the Substance, reduced spleen weights were observed in both sexes in the OECD TG 412 study, although there was no concentration-response relationship.

Furthermore, existing information on exposure to PFOA, PFOS and HFPO-DA indicate impaired functionality of the immune system, measured by reduced T cell dependent antibody responses (TDAR) (Rushing, 2017[4]; EFSA, 2020[2]).

Liver peroxisome proliferation is an indicator for the peroxisome proliferator-activated receptor alpha (PPARα) induction. Many PFAS are ligands of the PPARα (EFSA, 2020[2]). It has been shown that upon exposure to HFPO-DA, both maternal and foetal livers show

[2] European Food Safety Authority (EFSA). 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. Retrieved from https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2020.6223
[3] European Chemical Agency (ECHA). 2019. SVHC SUPPORT DOCUMENT - HFPO-DA AND ITS SALTS/ACYL HALIDES. Retrieved from https://echa.europa.eu/documents/10162/53fa6a5b-e95f-3128-ea9d-fa27f43b18bc
[4] Rushing, B. R. *et al*. (2017) Evaluation of the immunomodulatory effects of 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in C57BL/6 mice. Toxicol Sci, 156, 179-189

upregulation of genes associated with the PPAR signalling pathway (Conley, 2019[5]), indicating that HFPO-DA is bioavailable to the foetus.

Other, non-PFAS PPARα agonists have been shown for example to suppress the acute phase response, an important component of inflammatory and immune responses (Gervois, 2004[6]), and to be involved in the phenotypic changes of macrophages (reviewed in Christofides, 2021[7]).

Even though no mode of action of immunotoxicity by PFAS has been established, the available data on PFOS and PFOA suggests that their immunotoxic effects may originate from modulation of PPARs, NF-κB regulated gene transactivation and/or regulation of apoptosis (EFSA, 2020[2]). There is thus a concern that PPARα agonism, and hence peroxisome proliferation, is directly associated with immune perturbation.

Based on the structural analogy, including information on functional impairment of the immune system, there is a particular concern for (developmental) immunotoxicity for the Substance.

For the reasons stated above, the developmental immunotoxicity Cohort 3 must be conducted.

In your comments on the proposed amendment, you agree to conduct Cohort 3.

2.3 Outcome

Under Article 40(3)(b) your testing proposal is accepted under modified conditions and you are requested to conduct the test with the Substance, as specified above.

Further expansion of the study design

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) were identified. However, you may expand the study by including the extension of Cohort 1B and/or Cohorts 2A and 2B if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance R.7a, Section R.7.6.

In your comments on the proposed amendment, you indicate your intention to include Cohorts 2A and 2B (developmental neurotoxicity) in the study design. ECHA reiterates that currently no triggers for the inclusion of cohorts 2A and 2B have been identified. However, the study may be expanded by including Cohorts 2A and 2B, provided it can be demonstrated that this is justified for scientific reasons as explained above.

[5] Conley, J. M. *et al*. (2019) Adverse Maternal, Fetal, and Postnatal Effects of Hexafluoropropylene Oxide Dimer Acid (GenX) from Oral Gestational Exposure in Sprague-Dawley Rats. EHP,127, 037008.
[6] Gervois, P. *et al*. (2004) Global suppression of IL-6-induced acute phase response gene expression after chronic in vivo treatment with the peroxisome proliferatoractivated receptor-α activator fenofibrate. J Biol Chem, 279, 16154-16160.
[7] Christofides A. *et al*. (2021) The role of peroxisome proliferator-activated receptors (PPAR) in immune responses, Metabolism, Volume 114, 2021, 154338, ISSN 0026-0495, https://doi.org/10.1016/j.metabol.2020.154338.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[8].

B. Test material

1. Selection of the Test material(s)

   The Test material used to generate the new data must be selected taking into account the following:
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test material must contain that constituent/ impurity.

2. Information on the Test material needed in the updated dossier
   - You must report the composition of the Test material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[9].

[8] https://echa.europa.eu/practical-guides
[9] https://echa.europa.eu/manuals

Appendix C: Procedure

ECHA received your testing proposal(s) on 9 February 2021 and started the testing proposal evaluation in accordance with Article 40(1).

ECHA held a third party consultation for the testing proposal(s) from 22 April 2021 until 7 June 2021. ECHA did not receive information from third parties.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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

ECHA did not receive any comments within the commenting period.

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

Deadline

In your comments on the proposed amendment, you requested an extension of the deadline to provide information from 30 to 42 months from the date of adoption of the decision. Upon request, you provided documentary evidence from a test laboratory.

On this basis, ECHA has granted the request and extended the deadline to 42 months.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-76 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix D: List of references - ECHA Guidance[10] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[11]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[12]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

[10] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[11] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[12] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[13]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

[13] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.