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EUROPEAN CHEMICALS AGENCY

Helsinki, 7 July 2017

Substance name: Hexafluoropropene
EC number: 204-127-4
CAS number: 116-15-4
Date of Latest submission(s) considered[1]: 22 December 2016
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of hexafluoropropene

DECISION ON SUBSTANCE EVALUATION

1. Requested information

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following information on the registered substance:

1.1 *In vitro* mammalian cell micronucleus test with fluorescence *in situ* hybridization (FISH) or immunochemical labelling of kinetochores (CREST) (OECD 487 /EU B.49)

You shall provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the Chemical Safety Report by **15 October 2018**. The deadline takes into account the time that you, the Registrant(s), may need to agree on who is to perform any required tests.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

2. Who performs the testing

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all Registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

3. Appeal

You can appeal this decision 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[3] by Claudio Carlon, Head of Unit of Evaluation 2

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[1] This decision is based on the registration dossier(s) at the end of the 12 month evaluation period.

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

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

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Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on hexafluoropropene and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority (eMSCA) to complete the evaluation of whether the substance constitutes a risk to human health. The eMSCA will subsequently review the information you submit and evaluate if further information should be requested in order to clarify the concern for mutagenicity/carcinogenicity.

1.1 *In vitro* mammalian cell micronucleus test with fluorescent *in situ* hybridization (FISH) or immunochemical labelling of kinetochores (CREST) (OECD 487 /EU B.49)

The concern(s) identified

The genotoxic potential of the substance was assessed both *in vitro* and *in vivo*. Negative results were obtained in the Ames test and in gene mutation assay both in presence and in absence of metabolic activation. In a mammalian chromosome aberration study in CHO cells, results reported as positive (with and without metabolic activation) were observed. However, ECHA 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 as a result of cytotoxicity.

You updated the *in vivo* data before this evaluation and the results are the following:

Two *in vivo* micronucleus studies were presented: one with results reported as positive only in the high dose group in the male mice and concluded by you as negative ([redacted] 1986) and considered by ECHA as potentially false positive and one with negative results ([redacted] 1993); an unscheduled DNA synthesis (UDS) study with negative results; a dominant lethal mutation in rats with negative results.

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, specifically related to chromosome aberrations, is to be considered inconclusive and further experimental data are needed to clarify the concern for genotoxicity which could also inform on the potential mode of action.

Pending on the results of the studies required, the potential need of derivation of a derived minimum effect level (DMEL) instead of a derived no effect level (DNEL) could significantly influence the elaboration of the exposure scenarios in the registration dossier(s).In case of positive results in *the in vitro* studies requested in this decision, the Registrant(s) be asked to perform the two *in vivo* studies (*in vivo* Comet assay and *in vivo* micronucleus test) pursuant to Article 46(3) of the REACH Regulation eventually resulting in a harmonised classification for mutagenicity of the substance under Regulation (EC) No 1272/2008.

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Why new information is needed

An *in vitro* micronucleus test performed according to the current OECD 487 is requested to verify the genotoxic effect observed *in vitro* and the possible role of cytotoxicity. An analysis by FISH or CREST of the micronucleus observed is requested in order to clarify, if the outcome is the result of clastogenic and/or aneugenic events. In case of positive results in this *in vitro* test, an appropriate *in vivo* follow-up study will be requested in a subsequent substance evaluation decision to clarify the concern for germ cell mutagenicity and if adequate risk management measures have to be taken (e.g. classification proposal).

You disagreed with the eMSCA conclusion and asked not to perform the new *in vitro* test on the basis of the available data suggesting a weight-of-evidence assessment of hexafluoropropene genotoxicity. However ECHA deems that, in the presence of uncertainties regarding the reliability of the data addressing chromosome aberrations, your application of the weight-of-evidence approach and the conclusion that "the substance is likely not genotoxic" is uncertain as described above. Therefore in order to clarify the concern for genotoxicity, ECHA considers that further information is necessary.

Alternative approaches and proportionality of the request

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 to and conforming with the appropriate rules in the respective annex, and an adequate and reliable documentation.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the registered substance subject to this decision: *In vitro* mammalian cell micronucleus test with fluorescent *in situ* hybridization (FISH) or immunochemical labelling of kinetochores (CREST) (OECD 487 /EU B.49).

Remaining concerns

Mutagenicity

In case of positive results in this *in vitro* test, an appropriate *in vivo* follow-up will be requested.

Carcinogenicity

No carcinogenicity studies are available on hexafluoropropene . You self-classified the substance with a carcinogenicity category 2 classification (suspected carcinogen).

However, a structurally-related substance, tetrafluoroethylene (TFE), increased combined incidence of benign and malignant kidney tumors in rat of both sexes and caused mononuclear-cell leukemia. Based on this, the International Agency for Research

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on Cancer (IARC) has recently assessed this substance and concluded that it is probably carcinogenic to humans (Group 2A) (IARC Monographs, Volume 110, 2016). It is noted that tetrafluoroethylene is already self-classified under Regulation (EC) No 1272/2008 (the CLP Regulation) by many notifiers as Carc cat 1B. The kidney-specific carcinogenicity of tetrafluoroethylene is most likely related to the selective uptake and consequent processing of TFE-glutathione conjugates by renal β-lyase. For hexafluoropropene kidney has also been identified as the target organ and also the hexafluoropropene conjugation with glutathione (GSH) has been experimentally demonstrated.

In addition, other structurally similar substances have been classified for carcinogenicity (e.g. trichloroethylene CAS 79-01-6, classified as Carc 1B; tetrachloroethylene CAS 127-18-4, classified as Carc 2).

Therefore, a further evaluation of the carcinogenicity of the registered substance subject to the present decision is needed (see below).

Note for your consideration

For the remaining concerns, you are invited to take the following into account for the follow-up of the current substance evaluation:

In line with Article 46(3) of the REACH Regulation, the eMSCA will examine any information submitted in response to this decision. At the follow-up stage, the eMSCA will also assess the potential carcinogenicity and the associated risks of the registered substance and consider preparing a further draft decision to clarify that concern. In this follow-up assessment, the eMSCA will take into account, among other things:

- the mode of action (possible genotoxicity and formation of metabolites of concern, in particular relevant to kidney),
- results from relevant recently performed tests and assessments,
- read-across from structurally similar substances,
- any relevant information to further support the exposure assessment, in particular for man via the environment (e.g. emission data, monitoring data),
- the relevance of risk management measures.

You are invited to take these parameters into account for the follow-up of the current substance evaluation and to provide any further assessment/information in your updated registration dossier.

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/Suspected C and R; High (aggregated) tonnage, Hexafluoropropene, CAS No 116-15-4 (EC No 204-127-4) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2015. The updated CoRAP was published on the ECHA website on 17 March 2015. The Competent Authority of Italy (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your Registration(s) and other relevant and available information.

The evaluating MSCA used a step-wise approach in order to clarify the concern for mutagenicity (*in vitro* tests). 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.

Registrant(s)' commenting phase

On 26 April 2016, ECHA sent the draft decision to you and invited you pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision. This deadline included an extra seven-day period as addressed in the last update point 9(d) of the Terms of Conditions of REACH-IT.

On 1 June 2016, you submitted your comments to ECHA.

Proposals for amendment by other MSCAs and ECHA and referral to Member State Committee

The evaluating MSCA notified the draft decision to the Competent Authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the Reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s).

Your comments on the proposed amendment(s) were taken into account by the Member State Committee and are reflected in the Reasons (Appendix 1).

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-54 meeting and ECHA took the decision according to Article 52(2) and 51(6) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. 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.

3. In relation to the required experimental study/ies, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

   Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the stud(y/ies) on behalf of all of them.