~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: CCH-D-0000001396-72-03/F Helsinki, 22 March 2011

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 2,3,3,3-tetrafluoropropene, CAS 754-12-1 (EC No 468-710-7), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation) the European Chemicals Agency (ECHA) has performed a compliance check of the registration dossier for **2,3,3,3-tetrafluoropropene, CAS 754-12-1 (EC No 468-710-7)** submitted by [redacted] (the Registrant), latest submission number [redacted] for above 1000 tonnes per year.

The compliance check was initiated on 26 April 2010.

On 19 August 2010, ECHA notified the Registrant of its draft decision and invited him to provide comments.

On 17 September 2010, the Registrant provided comments on the draft decision to ECHA. On 30 September 2010, the Registrant provided an updated IUCLID file to ECHA. ECHA has considered the information received and amended the draft decision accordingly.

On 29 October 2010, ECHA notified the Member State Competent Authorities of its draft decision and invited them to propose amendments and to comment on the draft decision.

By 28 November 2010, Member State Competent Authorities submitted proposals for amendment and comments on the draft decision.

On 1 December 2010, ECHA notified the Registrant of the proposals for amendment for its draft decision and invited him to provide comments on these proposals. ECHA has

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considered the proposed amendments received and amended the draft decision accordingly.

On 13 December 2010, the draft decision was referred to the Member State Committee.

On 21 December 2010, the Registrant provided comments on the proposals for amendment and on other issues.

The Member State Committee took the comments of the Registrant into account. After discussion in the Member State Committee meeting on 1-3 February 2011, the amended draft decision was modified by the Member State Committee and a unanimous agreement of the Member State Committee on the amended and modified draft decision was reached on 3 February 2011.

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

II. Information required

ECHA has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of the REACH Regulation.

1) Pursuant to Articles 41(1)(a), 41(3), 3(28), 10(a)(vii), 12(1) as well as Annexes I, 1.1.4 and X of the REACH Regulation, the Registrant shall submit for the registered substance robust study summaries for the following studies:

   a. "Inhalatory two-generation reproduction toxicity study with HFO-1234yf [redacted] rats", Company study number [redacted] for meeting the information requirement of Annex IX, 8.7.3 of the REACH Regulation. The detailed summary of the methods and results is inadequate, and occasionally inconsistent. The Registrant is accordingly requested to upgrade the robust study summary for this endpoint.
   b. "Prenatal developmental inhalation toxicity study with HFO-1234yf in rats", Company study number [redacted], for meeting the information requirement of Annex IX, 8.7.2 of the REACH Regulation. The detailed summary of the methods and results is inadequate. The Registrant is accordingly requested to upgrade the robust study summary for this endpoint.
   c. "Inhalation prenatal developmental toxicity study of HFO-1234yf (2,3,3,3-tetrafluoropropene) in rabbits", Company study number [redacted], for meeting the information requirement of Annex X, 8.7.2 of the REACH Regulation. The detailed summary of the methods and results is inadequate. The Registrant is accordingly requested to upgrade the robust study summary for this endpoint.

2) Pursuant to Articles 41(1)(a), 41(3), 10(a)(vi) and (vii), 12(1)(e) and Article 13(3) as well as Annex X, 8.6.4 of the REACH Regulation, the Registrant shall submit the following information using the test method as indicated below.

   - 90-day repeated dose toxicity study (Annex X, 8.6.4. REACH Regulation) in the rabbit, by inhalation (method B.29 of Regulation (EC) No 440/2008 or OECD 413). The study protocol shall be modified with additional clinical pathology and histopathological evaluations to evaluate effects on

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reproductive organs; specifically as described in OECD 416, paragraphs 29-32, 39, 41-45.

3) Pursuant to Articles 41(1)(a), 41(3), 14(1), 14(3), 14(4) and Annex I, of the REACH Regulation, the Registrant shall submit the information indicated below.

   a. Derived No Effect Level (DNEL) for consumers (Article 14(3)(a) and Annex I, section 1.4).
   b. Exposure assessment, including the generation of exposure scenario(s) and exposure estimation for consumer use (Article 14(4)(a) and Annex I, section 5). Consumer use should include scenarios such as leakage from [redacted], and amateur use in [redacted].

Pursuant to Article 41(4) of the REACH Regulation, the Registrant shall submit the information referred to in points 1) and 3) above in the form of an updated IUCLID dossier to ECHA by **12 months from the date of the decision, i.e. on 22 March 2012.**
The Registrant shall submit the information referred to in point 2) above in the form of an updated IUCLID dossier to ECHA by **24 months from the date of the decision, i.e. on 22 March 2013.**

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance in accordance with **Article 6** of the REACH Regulation, does not comply with the requirements of Articles **10, 12, 13 and 14 and with Annexes I and X** thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

1) Robust study summaries

Pursuant to Articles 10(a)(vii) and 3(28) as well as Annex I, 1.1.4 of the REACH Regulation, the technical dossier of the registration shall include robust study summaries. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. A guide to the preparation of robust study summaries is provided at: http://echa.europa.eu/doc/publications/practical_guides/pg_report_robust_study_summaries.pdf

The Registrant has not reported in the IUCLID format robust study summaries within the meaning of Article 3(28) of the REACH Regulation for the following studies:

a. "Inhalatory two-generation reproduction toxicity study with HFO-1234yf [redacted] rats", Company study number [redacted], for meeting the information requirement of Annex IX, 8.7.3 of the REACH Regulation. ECHA remains of the opinion that the revised robust study summary in the updated dossier is inadequate because the detailed summary of the methods and results is inadequate, and occasionally inconsistent. For example, the Registrant fails to provide summary values (mean and standard deviation) for parameters which show statistically-significant effects, in failing to provide the detailed statistical analysis (methods and results) of the covariance of body weight with delay in vaginal opening, in failing to mention that vaginal opening is delayed at

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15000ppm with statistical significance, and in warranting that there are no effects where there are statistically-significant effects. The Registrant is accordingly requested to upgrade the robust study summary for this endpoint.

b. "Prenatal developmental inhalation toxicity study with HFO-1234yf in rats", Company study number [redacted] for meeting the information requirement of Annex IX, 8.7.2 of the REACH Regulation. ECHA remains of the opinion that the revised robust study summary in the updated dossier is inadequate because the detailed summary of the methods and results is inadequate. For example, the report is sometimes ambiguous as to whether "increases" are statistically-significant or not, insufficient data are presented on the incidence and quantification of findings, and some phrases are incomprehensible to ECHA. The Registrant is accordingly requested to upgrade the robust study summary for this endpoint.
c. "Inhalation prenatal developmental toxicity study of HFO-1234yf (2,3,3,3-tetrafluoropropene) in rabbits", Company study number [redacted], for meeting the information requirement of Annex X, 8.7.2 of the REACH Regulation. The detailed summary of the methods and results is inadequate. For example, no information is given on the chronology of death or euthanasia, and quantitative data on parameters such as mean body weight gain/ loss and food consumption are not given. Such information is essential for understanding the Registrant's conclusions. The Registrant is accordingly requested to upgrade the robust study summary for this endpoint.

Therefore, the Registrant is required to provide robust study summaries of all studies listed above.

2) 90-day repeated dose toxicity study in rabbits

Pursuant to Articles 41(1)(a), 41(3), 10(a)(vi) and (vii), 12(1)(e) and Annex X, section 8.6.4, ECHA may require further tests in the case that there is toxicity of particular concern, or indications of an effect for which the available evidence is inadequate for toxicological evaluation and/ or risk characterisation. The results presented in the Registrant's prenatal developmental toxicity testing on rabbits satisfy these criteria. The death of the pregnant rabbits satisfies the criterion, "toxicity of particular concern", as it is a severe effect. The available evidence is inadequate for toxicological evaluation and/ or risk characterisation because the data show that rabbit is much more sensitive to toxicity from 2,3,3,3-tetrafluoropropene, as compared with the rat. The ECHA's guidance (R.7, page 323) provides that "*Studies on the most sensitive animal species should be selected as the significant ones, unless toxicokinetic and toxicodynamic data show that this species is less relevant for human risk assessment.*" Given that the data show a species difference in sensitivity, it is appropriate to request information for the most sensitive species, the rabbit. The available information on the toxicity of 2,3,3,3-tetrafluoropropene on the rabbit is inadequate for toxicological evaluation and/ or risk characterisation for several reasons, including that there is only one study (a developmental toxicity study), that the characterisation of toxicity in the adult animals is inadequate (e.g. lacking histopathological examination), that the exposure scenario is too short to be reliably extrapolated for long-term exposure, and that the information in rabbit does not cover the fertility endpoint for the reproductive toxicity information requirement.

ECHA has considered the Registrant's arguments in the comment, and the proposed studies on acute toxicity and biotransformation of 2,3,3,3-tetrafluoropropene. ECHA considers that the Registrant's proposed studies do not meet the need for characterisation of the sub-chronic toxicity of the 2,3,3,3-tetrafluoropropene in the most sensitive species, the rabbit. Specifically, the Registrant proposes metabolism and acute toxicity studies, which (a) do not characterise the sub-chronic toxicity of the substance and (b) would be of uncertain

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relevance to the sub-chronic toxicity of the substance, since it is not yet established that the mechanism of toxicity is the same in acute and sub-chronic toxicity of the substance. ECHA believes that the proposed 90-day inhalation study in rabbit is technically feasible.

The Registrant is accordingly requested to submit the information using the test method: 90-day repeated dose toxicity study (sub-chronic toxicity study) in the rabbit, by inhalation (method B.29 of Regulation (EC) No 440/2008 or OECD 413). The study protocol shall be modified with additional clinical pathology and histopathological evaluations to evaluate effects on reproductive organs; specifically as described in OECD 416, paragraphs 29-32, 39, 41-45. This modification is to enable the study to examine effects of 2,3,3,3-tetrafluoropropene on male and female sexual organs and their function, as partial coverage of the fertility endpoint for the reproductive toxicity information requirement (Annex X, 8.7.3) in the most sensitive species, the rabbit. The Registrant is requested to update the dossier with the relevant information.

3) Missing information related to Chemical Safety Report

Pursuant to Articles 41(1)(a), 41(3), 14(1), 14(3), 14(4) and Annex I of the REACH Regulation, a Chemical Safety Report shall be provided. Annex I sets out the general provisions for assessing substances and preparing Chemical Safety Reports (CSR).

a. Derived no effect level (DNEL)

Article 14(3)(a) and Annex I, section 1.4 of the REACH Regulation, require the registrant to establish DNEL(s) for the registered substance for consumers, where appropriate. The CSR under IUCLID section 5.11.3, does not contain a DNEL for effects on the general population (consumers). Since [redacted] are applications with wide dispersive use, consumer exposure can be anticipated, and the Registrant's exposure assessment predicts that there will be exposure, albeit at levels below 1ppm. The Registrant is accordingly requested to establish the appropriate DNEL and to update the CSR as necessary.

b. Exposure

The substance is classified by the Registrant as a Category 1 flammable gas. Article 14(4)(a) and Annex I, section 5 of the REACH Regulation requires the registrant to generate exposure scenarios and exposure estimations for the registered substance. Since [redacted] an application with wide dispersive use, consumer exposure can be anticipated. We note that the Registrant has, in the comment and the revised dossier, considered consumer exposure for scenarios such as [redacted] and has excluded consumer/ amateur [redacted] as an allowed use. However, we note that "reasonably foreseeable" exposure must be characterised, and this would also include accidental [redacted]

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IV. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that reads:

> "*Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable.*"

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2008 adapted to the technical progress by Commission Regulation (EC) No 761/2009 and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Done at Helsinki,

[redacted]

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