~~CONFIDENTIAL~~

European Chemicals Agency

For final decision: TPE-D-0000001721-81-03/F Helsinki, 16/09/2011

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For [redacted] [3-Pentanone, 1,1,1,2,2,4,5,5-nonafluoro-4-(trifluoromethyl)-], CAS [redacted] (EC No 436-710-6), 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 40(1) of the REACH Regulation, ECHA has examined a testing proposal set out in the registration dossier for [redacted] **[3-Pentanone, 1,1,1,2,2,4,5,5-nonafluoro-4-(trifluoromethyl)-], CAS [redacted] (EC No 436-710-6)** submitted by [redacted] (Registrant), latest submission number [redacted]

In accordance with Articles 10(a)(ix) and 12(1)(d) of the REACH Regulation, the Registrant submitted the following testing proposal as part of the registration dossier to fulfil the information requirements set out in Annex IX:

Pre-natal developmental toxicity study (EU test method B.31)

The examination of the testing proposal was initiated upon the date when receipt of the complete registration dossier was confirmed on 21 December 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 15 March until 29 April 2011. ECHA received the comments from third parties concerning the use of existing reproduction/developmental toxicity screening study, 28-day and 90-day repeated dose toxicity studies, *in vitro* testing and QSAR modelling, and the use of TTC (Threshold of Toxicological Concern) concept. More information is provided in the section III, statement of reasons below.

On 16 June 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 18 July 2011 the Registrant did not provide to ECHA any comments on the draft decision.

On 29 July 2011 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days.

Subsequently, Competent Authorities of the Member States did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the requirements of the REACH Regulation. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

II. Testing required

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following test using the indicated test method:

- Pre-natal developmental toxicity study (Annex IX, 8.7.2, method B.31 of Regulation (EC) No 440/2008, OECD test guideline 414) in rat by the inhalation route

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by 16 March 2013 - 18 months from the date of decision an update of the registration dossier containing the information required by this decision. In this dossier update the Registrant shall make a proposal on another pre-natal developmental toxicity study on a second species, if considered necessary based on performed studies and all other relevant data.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal of the Registrant for the registered substance and scientific information submitted by third parties. A pre-natal developmental toxicity study in one species is required under Annex IX, 8.7.2 of the REACH Regulation and on a second species under Annexes IX and X, 8.7.2, subject to all appropriate column 2 or Annex XI data adaptations. Since information on this endpoint is missing in the registration dossier, and since no acceptable adaptations to omit this information requirement have been received, ECHA accepts the proposed test. Since the substance is a volatile liquid and all repeated dose studies submitted by the Registrant have been conducted by the inhalation route, the test shall be carried out in rat by the inhalation route using the EU test method B.31. The decision on the need to perform another pre-natal developmental toxicity study on a second species shall be based on the outcome of the first developmental study and all other relevant available data (Annex IX, 8.7.2 of the REACH Regulation).

The third party information following the public consultation was evaluated in order to determine whether there is already scientifically valid information that addresses the relevant substance and hazard endpoint. This additional information does not, however, change the conclusion that a pre-natal developmental toxicity study needs to be requested, as explained below.

Before conducting a pre-natal developmental toxicity study (OECD Guideline 414), the third party proposes to consider the following alternative testing strategies and use results to waive the test.

i. The third party refers to Annex IX, Column 2, 8.7 and states that no pre-natal developmental toxicity study should be performed if:
   - no treatment-related adverse effects, including those in male and female reproductive organs, are observed in repeated dose studies (28-day or 90-day), or in existing screening test;
   - no evidence of toxicity seen in any of the test available;
   - molecular weight, physico-chemical characteristics (e.g. water solubility, log Kow, granulometry) and acute toxicity data indicate a low systemic absorption is likely;
   - industrial use e.g. in closed systems and no consumer use indicate no significant human exposure.

   ECHA points out that treatment-related effects were observed both in 28-day and 90-day studies indicating also that the substance is absorbed. The reproductive/developmental toxicity screening test (OECD 421) is neither an alternative to the developmental toxicity test proposed nor does it replace the information requirements for this test. Due to test design (e.g. small number of animals, selectivity of the endpoints, and different dosing regime) of the screening test, negative results do not provide sufficient level of certainty with respect to developmental toxicity. In addition, skeletal and soft tissue alterations are not examined in the screening test. Moreover, the study is requested under Annex VIII, 8.7.1. to the REACH Regulation, and it cannot be used to adapt the standard information requirement for developmental toxicity even though *vice versa* the screening test can be omitted pursuant to column 2 of Annex VIII, 8.7.1. if a pre-natal developmental toxicity study is available.

   The criteria of Annex IX, Column 2, 8.7 to adapt the standard information requirements for developmental toxicity are not met as the treatment-related effects were observed, the substance is absorbed. In addition, ECHA considers that the Registrant has stated that exposure arises when the substance is used in batch and other processes. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

ii. The third party has proposed two types of information for ECHA to consider, i.e. the use of *in vitro* testing and of TTC concept. In addition, the third party states that "it is desirable that the registrant retrieves and submits occupational exposure and *in vivo* toxicokinetics data, especially relevant for professional use, which can demonstrate that no systemic absorption occurs via relevant routes of exposure and that this information and other existing toxicological data are thoroughly evaluated".

Considering that ECHA invited submission of "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal", as specified by Article 40(2), ECHA has evaluated the information provided by the third party. ECHA has concluded that the proposed information does not sufficiently address the relevant endpoint. Consequently, ECHA concludes that the information provided is not a basis for rejecting the testing proposed.

iii. The third party has submitted CAESAR prediction (QSAR model for pre-natal developmental toxicity). According to the information, the substance was predicted to be developmental non-toxicant.

ECHA notes that it is stated in the third party comment that the prediction might be outside the applicability domain. In addition, the compliance with Annex XI, Section 1.3 requirements of the method used could not be established by ECHA as information concerning the validity of the method and adequacy for the purpose of classification and labelling and/or risk characterisation, and documentation on the model used was not provided.

Therefore, ECHA concludes that the information submitted does not meet the conditions for the adaptation on the basis of methods set out in Annex XI, Sections 1.2, 1.3 or 1.4 Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

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 1907/2006 as adapted to technical progress 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 appeal shall be lodged within three

months of receiving notification of this decision. Further information on the appeal procedure can be found on the 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]

Jukka Malm
Director of Regulatory Affairs