~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: CCH-D-0000001716-72-04/F Helsinki, 24/10/2011

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

For dipropylene glycol methyl ether acetate, CAS 88917-22-0 (EC No 406-880-6), 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 (the REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation, ECHA has performed a compliance check of the registration dossier for ***dipropylene glycol methyl ether acetate***, CAS 88917-22-0 (EC No 406-880-6) submitted by [redacted] (Registrant), latest submission number [redacted] for [redacted] tonnes per year.

The compliance check was initiated on 21 June 2010.

The draft decision was notified to the Registrant on 3 November 2010.

The Registrant submitted comments on the draft decision on 29 November 2010. The Registrant submitted an updated dossier containing new information on 31 March 2011. ECHA has considered the information received and amended the draft decision accordingly.

On 17 June 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 submitted proposals for amendments to the draft decision.

On 20 July 2011 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification.

ECHA has reviewed the proposals for amendment received and has not modified the draft decision.

On 1 August 2011 the draft decision was referred to the Member State Committee.

On 16 August 2011 the Registrant provided comments on the proposals for amendment.

The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 20-23 September 2011, the draft decision was modified by the Member State Committee and a unanimous agreement of the Member State Committee on the modified draft decision was reached on 23 September 2011.

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

II. Information required

Pursuant to Articles 41(1)(a), 41(1)(b), 41(3), 10(a)(vii), 12(1)(d) and 13, as well as Annexes VIII, IX, and XI of the REACH Regulation, the Registrant shall submit the information for the registered substance using the indicated test method:

- An *in vitro* gene mutation on mammalian cells, (Annex VIII, 8.4.3.of the REACH Regulation), using test method B.17 according to Commission Regulation (EC) No 440/2008; and
- A pre-natal developmental toxicity study, (Annex IX, 8.7.2. of the REACH Regulation), in the rat, by the oral route, using test method B.31 according to Commission Regulation (EC) No 440/2008 or OECD 414.

Pursuant to Article 41(4) of the REACH Regulation, the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by 24 October 2012 - **12 months from date of decision**.

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 and 13 and with Annexes VIII, IX, and XI 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.

Pursuant to Articles 10(a)(vii) and 12(1)(d) of the REACH Regulation, a registration for a substance produced in quantities of 100-1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX.

a. The technical dossier is missing information on the endpoint:

- *In vitro* gene mutation in mammalian cells (Annex VIII, 8.4.3 of the REACH Regulation)

The REACH Regulation (Annex VIII, 8.4.3) requires an *in vitro* gene mutation study in mammalian cells if negative results are obtained in the tests in Annex VII, 8.4.1. and Annex VIII, 8.4.2.

The technical dossier submitted by the Registrant contains the results of two *in vitro* gene mutation studies in bacteria (Annex VII, 8.4.1) on the registered substance showing negative results, an *in vitro* mammalian chromosome aberration test on the registered substance showing negative results (Annex VIII, 8.4.2), and statements for the use of read-across from the results of a yeast cytogenetic assay on dipropylene glycol methyl ether (DPM) showing negative results.

The Registrant is accordingly requested to submit the missing information on *in vitro* gene mutation in mammalian cells, performed with the registered substance. The recommended test method is B.17 according to Commission Regulation (EC) No 440/2008.

b. The technical dossier contains statements for the use of a read-across approach from a supporting substance for the registered substance for the endpoint on:

- Pre-natal developmental toxicity study (Annex IX, 8.7.2 of the REACH Regulation)

In the description of identified uses in section 3.5 "Identified uses" of the IUCLID dossier, the Registrant indicates dermal and inhalation as significant routes of human exposure.

The technical dossier contains the results of two pre-natal developmental toxicity studies, one in the rat and one in the rabbit, by the inhalation route for dipropylene glycol methyl ether (DPM) as a surrogate for dipropylene glycol methyl ether acetate (DPMA). These two studies are marked as the key studies for this endpoint. The Registrant suggests a read-across for the results of these studies on DPM to the registered substance with the justification that DPMA is expected to rapidly hydrolyse to DPM. In addition there are two pre-natal developmental toxicity studies, marked as supporting studies on the surrogate propylene glycol monomethyl ether (PM).

The updated technical dossier contains new information. After evaluating the updated dossier, ECHA notes the following:

- The Registrant expects the compound DPM to be the breakdown product resulting from the hydrolysis of DPMA, and argues that because

the breakdown of DPMA is rapid, the toxicological properties of DPMA can be read-across from DPM. In the new *in vitro* toxicokinetic study submitted, the registered substance DPMA hydrolyses in plasma with a half life of 11-17 minutes, and in rat liver S9 fractions with a half life of 40-82 minutes.

In the view of ECHA the new toxicokinetic data suggest that the registered substance, DPMA, will be available in the body for significant amounts of time. For example, using the plasma half life of 12 minutes and assuming 100% absorption, then >10% of the substance DPMA will be available for >36 minutes. Given an oral gavage dose of 1g/kg, this would suggest that >100mg/kg of DPMA is available in the body for >36 minutes. Less conservative assumptions (e.g. partition to the liver or other tissue, where hydrolysis is significantly slower) could substantially increase the estimate of the concentration and period of time the parent substance is available in the body.

ECHA considers that the hydrolysis of DPMA is not sufficiently rapid to ensure that there is no systemic availability of this substance. The pre-natal developmental toxicity of DPMA is not addressed by the available information on DPM, and it is not possible to conclude that the DPMA would be unable to exert a toxic effect in the time that it is available in the body.

In conclusion, the Registrant has not established a basis for showing that DPMA (before hydrolysis) can be read-across to DPM for the endpoint on pre-natal developmental toxicity. Consequently, it is not possible to conclude that the human health effects of the registered substance may be predicted from data for the reference substance(s), and so a key requirement of Annex XI, 1.5 governing grouping of substances and read-across approach is not met.

- The registered substance DPMA contains an acetate functional group not present in the surrogate DPM. The Registrant argues in his comments on the draft decision that based on the expected hydrolysis of DPMA to DPM, the acetate functional group is not relevant for the read-across. However, given that the substance is expected to be available in the body for a significant time before hydrolysis as described above, the acetate functional group is of relevance to the read-across. Therefore, the basis for establishing similarity exemplified in Annex XI, 1.5(1) (common functional group) for grouping and read-across is not met.

Therefore, ECHA concludes that the suggested read-across is not acceptable for the endpoint on pre-natal developmental toxicity.

The Registrant is requested to submit the missing information on pre-natal developmental toxicity performed with the registered substance, in the rat, oral route, using test method B.31 according to Commission Regulation (EC) No 440/2008 or OECD 414.

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 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]

Jukka Malm
Director of Regulatory Affairs