Decision number TPE-D-0000000775-69-04/F Helsinki, 15 December 2009

DECISION
ON A TESTING PROPOSAL PURSUANT TO ARTICLE 40(3) REGULATION (EC) NO 1907/2006 (THE REACH REGULATION)

***SOYBEAN OIL, EPOXIDISED, REACTION PRODUCTS WITH METHANOL AND WATER* (EC Nr. 700-080-3), REGISTRATION NUMBER: [redacted]**

SUMMARY OF THE DECISION

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedures set out in Articles 50 and 51 of the REACH Regulation concerning the testing proposals for *Soybean oil, epoxidised, reaction products with methanol and water* (EC No. 700-080-3), provided [redacted] ("the registrant"):

a) Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA rejects the following test proposed by the registrant: Dissociation constants in water (OECD test guideline 112)
b) Pursuant to Article 40(3)(a) of the REACH Regulation the registrant must carry out the following test: Viscosity of liquids (OECD test guideline 114)
c) Pursuant to Article 40(3)(a) of the REACH Regulation the registrant must carry out the following test: *Daphnia magna* reproduction tests (method C.20 of Regulation 440/2008/EC; OECD test guideline 211)
d) Pursuant to Article 40(3)(c) of the REACH Regulation the registrant must carry out the following test: Sub-chronic oral toxicity test - repeated dose 90-day oral toxicity study in rodents (method B.26 of Regulation 440/2008/EC; OECD test guideline 408)
e) Pursuant to Article 40(3)(c) of the REACH Regulation the registrant must carry out the following test: Prenatal developmental toxicity study (method B.31 of Regulation 440/2008/EC; OECD test guideline 414)

Pursuant to Article 40(4) and Article 22 of the REACH Regulation, the registrant must submit to ECHA by 16 December 2011 an update of the registration containing the information required by this decision.

The reasons for the conclusions on the testing proposal are presented in the section headed "Decision by ECHA" below.

This decision does not imply that the information provided by the registrant in his registration dossier (and in particular the information in accordance with Annexes VII to VIII of the REACH Regulation) are in compliance with the REACH requirements. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

RECORD OF PROCEDURE

[redacted] (hereinafter referred to as "the registrant") submitted to ECHA a registration dossier for the substance *Soybean oil, epoxidised, reaction products with methanol and water* (EC Nr. 700-080-3) for tonnage band 100 – 1000 t/a. The registration number of this dossier is [redacted] and the registration date is 14 January, 2009. On 9 February, 2009 the registrant submitted testing proposals addressing the information requirements for three endpoints (submission number [redacted]).

On 27 July, 2009 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.

On 24 August, 2009 the registrant provided to ECHA comments on the draft decision.

ECHA reviewed the further information received and did not change the requirements of the draft decision but amended the statement of reasons accordingly.

On 10 September, 2009 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 comments and proposals for amendments on the draft decision.

On 13 October 2009 ECHA notified the registrant of the comments and proposals for amendment of 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 amendments received and has amended the draft decision accordingly on 26 October, 2009.

On 26 October, 2009 ECHA referred the draft decision to the MSC.

On 6 November, 2009 the registrant submitted comments on the proposals for amendments of the competent authorities of the Member States.

The Member State Committee took the comments of the registrant on the proposals for amendments of the competent authorities of Member States into account. After discussion in the Member State Committee meeting on 2-4 December 2009, the amended draft decision was modified by the Member State Committee and a unanimous agreement of the Member State Committee on the modified and amended draft decision was reached.

DECISION BY ECHA

Legal basis and addressee

This decision is adopted pursuant to Articles 40, 50(1) and 51 of the REACH Regulation.

The decision is addressed to [redacted] "the registrant")

Original proposal of the registrant

The registrant submitted the following testing proposals as part of the registration dossier for ***Soybean oil, epoxidised, reaction products with methanol and water*** (EC number: 700-080-3), to fulfil the information requirements set out in Annex IX, in accordance with Article 12(1)(d) of the REACH Regulation:

- testing proposal for dissociation constant (Dissociation constants in water: OECD test guideline 112);
- testing proposal for viscosity (Viscosity of liquids: OECD test guideline 114);
- testing proposal for aquatic toxicity (*Daphnia magna* reproduction test: C.20 of Regulation 440/2008/EC; OECD test guideline 211)

Decision and Statement of reasons

On the basis of the examination of the testing proposals in submission [redacted] ECHA has made the following decision:

Testing proposed by the registrant

a) Dissociation constant (Annex IX (7.16) of the REACH Regulation)

According to the REACH Regulation, at the tonnage level registered (≥ 100 t/a), information on dissociation constant is required (Annex IX (7.16) of the REACH Regulation). The registrant proposed a test to derive the Dissociation constant test in water (OECD test guideline 112). Based on the proposal for amendment from a Member State Competent Authority, the registrant commented that the dissociation constant can actually be estimated from QSAR, information which is apparently already available to the registrant.

ECHA therefore has decided, pursuant to Article 40(3)(d) of the REACH Regulation to reject the following test originally proposed by the registrant: Dissociation constants in water (OECD test guideline 112). The registrant is therefore reminded of his obligation according to Article 12(1) of the REACH Regulation to include all relevant and available information in his registration dossier and to update his registration dossier accordingly. This obligation also applies to any information derived from QSAR estimations.

b) Viscosity (Annex IX (7.17) of the REACH Regulation)

The test Viscosity of liquids: OECD test guideline 114, proposed by the registrant is considered to be adequate to fulfil the information requirement. According to the REACH Regulation, at the tonnage level registered (≥ 100 t/a), information on viscosity is required (Annex IX (7.17) of the REACH Regulation).

ECHA therefore has decided that pursuant to Article 40(3)(a) of the REACH Regulation the registrant must carry out the following test: Viscosity of liquids (OECD test guideline 114).

c) Aquatic toxicity (Annex IX (9.1.5) of the REACH Regulation)

The *Daphnia magna* reproduction test (C.20 of Regulation 440/2008/EC, OECD test guideline 211), proposed by the registrant is considered to be adequate to fulfil the information requirement. According to the REACH Regulation, at the tonnage level

registered (≥ 100 t/a), the long term toxicity testing on invertebrates is required (Annex IX (9.1.5.) of the REACH Regulation).

However, the registrant is reminded that given the complex nature of the registered substance and its degradation potential care would be needed to ensure that the test substance concentration is maintained and analysed during the study, having sufficient recovery efficiency of the analysis method and a relevant limit of determination.

ECHA therefore has decided that pursuant to Article 40(3)(a) of the REACH Regulation the registrant must carry out the following test: *Daphnia magna* reproduction test (C.20 of Regulation 440/2008/EC, OECD test guideline 211). In addition, the registrant must report on the parameters specified in the previous paragraph in the robust study summary for the *Daphnia magna* reproduction test.

Additional testing required

d) Repeated dose toxicity (Annex IX (8.6.2) of the REACH Regulation)

The registrant has proposed to adapt the required standard information according to Annex XI 1.5 (Grouping of substances and read-across approach) of the REACH Regulation. Registrants are generally obliged to clearly state the reasons for such adaptations to the standard testing regime and refer to the appropriate specific rule(s). For read-across, Annex XI 1.5 sets out rules on which similarities may be based on. ECHA considers that the registrant has failed to adequately justify why the rules on similarities set out in Annex XI 1.5 can be applied to the registered substance.

Rule 1 (common functional group)
The substance used for the purpose of read-across is *epoxidized soybean oil (ESBO),* EC Nr. 232-391-0. This substance differs from the registered substance with regard to relevant functional groups. [redacted]

Rule 2 (common breakdown products)
The registrant has argued that ESBO and the registered substance may have common breakdown products. The registered substance is a complex reaction product composed of many different constituents with largely differing molecular sizes and unknown detailed composition. It is therefore not obvious to assume that ESBO and the registered substance have common breakdown products. Neither the registration dossier nor the registrant's comments to the draft decision contain sufficient evidence on common breakdown products.

In its comments the registrant described theoretical hypotheses on common metabolic pathways for ESBO and the registered substance. The registrant indicated that some of the metabolites of the registered substance could be the same as the possible metabolites from ESBO. However, the registrant neither submitted experimental data nor other scientific evidence to sufficiently support this hypothesis. Possible kinetic differences, subsequent changes in metabolic products, and the consequences on proportions and bioavailability of breakdown products have not been considered. Furthermore, the theoretical considerations regarding the metabolic fate of the [redacted] constituents of the registered substance are inconclusive and not supported by any substance specific data.

Therefore, on the basis of the information provided in the registration dossier and the further information provided by the registrant in its comments to the draft decision, it must be concluded that the registrant has failed to provide sufficient evidence to show that the breakdown products of ESBO and the registered substance are likely to be similar with respect to their toxicity.

As explained in the Annex to this decision the registrant's comments of 6 November 2009 have not altered this conclusion.

Rule 3 (constant pattern in changing potency/properties)
As there is only one substance used for read-across, the third rule, i.e. 'a constant changing in pattern of the potency of the properties across a category' cannot be applied as supporting evidence for read-across in this case.

In conclusion, due to the reasons mentioned above, ECHA considers that the registrant has failed to adequately justify the proposed adaptation.

Based on the justifications outlined above, ECHA concludes that the information requirement for repeated dose toxicity is not fulfilled. According to the REACH Regulation, at the tonnage level registered (≥ 100 t/a), the sub-chronic toxicity study (90 day) is required (Annex IX (8.6.2.) of the REACH Regulation).

ECHA has therefore decided that pursuant to Article 40(3)(c) of the REACH Regulation the registrant must carry out the following test: Sub-chronic oral toxicity test repeated dose 90-day oral toxicity study in rodents (method B.26 of Regulation 440/2008/EC; OECD test guideline 408). The species used should be the rat.

e) Reproductive toxicity (Annex IX (8.7.2.) of the REACH Regulation)

The registrant has proposed to adapt the required standard information according to Annex XI 1.5 (Grouping of substances and read-across approach) of the REACH Regulation. The justification provided is based on the read-across with the substance *epoxidized soybean oil (ESBO),* EC: 232-391-0. For the same considerations set out in section (d) above, ECHA considers that the registrant failed to adequately justify why the rules on similarities set out in Annex XI 1.5 can be applied to the registered substance

Accordingly, ECHA concludes that the information requirement for reproductive toxicity is not fulfilled. According to the REACH Regulation, at the tonnage level registered (≥ 100 t/a), the pre-natal developmental toxicity study is required (Annex IX (8.7.2.)).

ECHA has therefore decided that pursuant to Article 40(3)(c) of the REACH Regulation the registrant must carry out the following test: Prenatal developmental toxicity study (method B.31 of Regulation 440/2008/EC; OECD test guideline 414), by oral route. The species used should be the rat.

Deadline for complying with the Decision

Pursuant to Article 40(4) and Article 22(2) of the REACH Regulation, the registrant must submit to ECHA by 16 December 2011 an update of the registration containing the information required by this decision.

FURTHER INSTRUCTIONS

Good Laboratory Practice

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

> "*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*."

National GLP Monitoring Authorities maintain lists of test facilities approved for conducting tests in accordance with GLP, including the tests for which the approval applies.

Rights of Appeal

Under Article 51(8) of the REACH Regulation, an appeal may be brought against this decision to the Board of Appeal of ECHA. Such an appeal must be brought within three months of receiving notification of this decision. The procedure for lodging an appeal is described in the Board of Appeal's "Temporary Guidelines on Appeals" that can be found at the ECHA website 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]

Geert Dancet
Executive Director

Annex Further analysis of the applicability of rule 2 (common breakdown products)

Further analysis of the applicability of rule 2 (common breakdown products)

[redacted]

On 6 November, the registrant further informed ECHA of an estimated [redacted] The registrant stated that this ether may give rise to metabolites that differ from those of the analogue substance epoxidised soybean oil (ESBO). The registrant did not provide any further information with regards to the fate and toxicity of such metabolites.

[redacted]

In addition, ECHA was informed that [redacted] are assumed to be formed from the registered substance through partial lipolysis in the gastrointestinal tract. The registrant had made the assumption that these substances would then be further metabolised to the corresponding [redacted]. The registrant further presumed that the [redacted]

While such a degradation mechanism seems plausible in principle, it is uncertain which fraction of the [redacted] would be metabolised via this pathway and how long it would take until the [redacted] are degraded to the [redacted] Only in case of immediate degradation of all [redacted] to their corresponding [redacted] and sufficient data on these metabolites the adverse effects of the [redacted] (or their absence) might be predicted (see also Annex IX, 8.6.2, column 2, third indent). It appears, however, unlikely that such an immediate degradation occurs.

The registrant states in his argumentation to ECHA that '*Absorption of normal dietary lipids involves initial partial lipolysis in the gastrointestinal tract, to produce a mixture of* [redacted] *which are then absorbed into the intestinal mucosa, where they are reassembled into* [redacted] *before being distributed systemically via the lymph system.*'

Systemic distribution via the lymph implies that the [redacted] are not rapidly [redacted] It is a condition for rapid degradation to occur, that the registered substance undergoes a 'first pass' effect. The 'first-pass' effect is a phenomenon of xenobiotic metabolism in the liver whereby the concentration of an orally administered xenobiotic is greatly reduced before it reaches the systemic circulation. This, however, would require secretion from the mucosa cell into the portal vein, and not into the lymph as assumed by the registrant. This assumption is in line with the well-known physiological fact that only short to medium chained lipids (<10-12 Carbon atoms) are directly transported via the portal vein -and not via the lymph- and the information provided in the registration dossier that the carbon chain length of fatty acids in [redacted] as well as ESBO "is equal to the starting material, soy bean oil, where the typical fatty acid distribution is about [redacted]
Another condition for rapid degradation by the liver first-pass effect would be that the liver is capable of metabolising a very great fraction of the substance as it passes through the liver.

As the registrant has not provided information about the kinetics of the de-alkylation process, it is also uncertain whether this second condition is met.

Conclusions

In assessing safety, one of the concerns is whether the [redacted] or the [redacted] are capable of interacting with the lipid metabolism, for example, by interfering with the synthesis, function or degradation of normal lipid compounds. Thus, it cannot be excluded that such interference could lead to adverse effects. As both of these compounds are major breakdown products of the registered substance but not of the analogue substance ESBO, ECHA cannot accept the read-across proposed by the registrant.