EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000005089-69-03/F Helsinki, 3 November 2014

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

For 2-Butanone, peroxide, CAS No 1338-23-4 (EC No 700-954-4), 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 the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for 2-Butanone, peroxide, CAS No 1338-23-4 (EC No 700-954-4), submitted by [redacted] (Registrant):

- 90-day oral toxicity study (OECD 408) in rats, oral route
- Developmental toxicity / teratogenicity study (OECD 414)

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 24 July 2014, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) 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 REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

The examination of the testing proposals was initiated upon the date when receipt of the complete substance identity information, allowing processing of the testing proposals, was confirmed on 03 December 2013.

ECHA held a third party consultation for the testing proposals from 19 December 2013 until 03 February 2014. ECHA received information from third parties (see section III below).

On 15 May 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

By 23 June 2014 the Registrant did not provide any comments on the draft decision to ECHA.

On 24 July 2014 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 for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408). It is at the Registrant's discretion to perform the intended additional examinations during the testing program.

2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414).

Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **10 November 2016** an update of the registration dossier containing the information required by this decision.

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.

Note for consideration by the Registrant

The Registrant 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.

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 the Member States.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

ECHA notes that the registered substance is composed of two peroxide constituents and two additives or stabilizers, added to reduce the potential explosion hazard of the peroxide constituents.

The Registrant stated that "*from an environmental, ecotoxicological and toxicological point of view these stabilizers are considered to have comparable profiles and the hazardous or dangerous profile of MEKP* [Methyl Ethyl Ketone Peroxide, the peroxide content of the registered substance] *can be reliably predicted from tests with either combination of MEKP*

and those solvents as those properties are trigged by the most reactive and potent compound MEKP."

ECHA agrees that the hazardous properties of the registered substance are driven by the peroxide components. However, ECHA notes that the Registrant did not specify in the testing proposals information on the test sample preparations in terms of additive concentrations and concentration of the peroxide components. Due to the above reasons the test material for the tests proposed shall meet the requirements as explained in Section IV below.

1. Sub-chronic toxicity study (90-day)

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A sub-chronic toxicity study (90-day) is a standard information requirement as laid down in Annex IX, section 8.6.2. of the REACH Regulation.

ECHA notes that the technical dossier contains an oral 28-day toxicity study in rats according to OECD Guideline 407 on the registered substance and two non-standard repeated dose toxicity studies by dermal application in rats and mice (exposure=13 weeks; reliability score=3).

Regarding the oral toxicity study in rats the Registrant stated that "*In the 28-day oral toxicity study the substance revealed a NOAEL of 65 mg/kg bw/day in male and female animals. MEKP caused a series of unspecific and minor alterations in general appearance (reduced-well being), in body weights, feed consumption, haematology, clinical biochemistry and organ weights."*

Furthermore, in relation to the dermal studies available in the dossier, the Registrant stated that "*As no NOAELs for local and systemic effects could be deduced from the studies due to the high corrosive effects of MEKP, the studies were not used for risk characterisation evaluation.*"

ECHA assessed the information present in the dossier and agrees with the Registrant's conclusion with regard to two non-standard dermal studies in rats and mice.

Therefore, ECHA concludes that the dossier does not contain information for the registered substance to meet the information requirements of Annex IX, Section 8.6.2. of the REACH Regulation and none of the column 2 specific rules for adaptation apply.

The Registrant has submitted a testing proposal for a sub-chronic toxicity study (90-day) in rats via the oral route (OECD Guideline 408), with the following justification: "*A 90 day oral toxicity study is not available and is thus proposed for MEKP in order to clarify the importance of the effects noted in the 28 day toxicity study. This 90-day toxicity study will include additional investigation on sexual organs to support the test proposal/strategy for reproductive toxicity.*"

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

The Registrant proposed testing via the oral route. In light of the physico-chemical properties and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate. Moreover, in accordance with paragraph 3 of Annex IX, *in vivo* testing with corrosive substances at concentration/dose level causing corrosivity shall be avoided and prior testing further guidance on testing strategies should be consulted in order to choose correct dosing level.

In relation to the Registrant proposal to extend the sub-chronic toxicity study (90-day) by including additional investigation on sexual organs, ECHA notes that it is at the Registrant's discretion to perform the intended additional examinations during the testing program and use the results to ensure the safe use of the substance. However, the Registrant is reminded that the proposed extension of this study does not fulfil the standard information requirements in the registration dossier for reproductive toxicity set out in Annex X, Section 8.7.3. unless the Registrant applies the results from the 90-day study as a valid adaptation according to Annex X, Section 8.7, column 2.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party suggested that "*On the basis of information presented in the Registration Dossier, the substance is expected to be readily hydrolysed after oral ingestion. The substance may therefore undergo immediate disintegration and not reach the blood without hydrolysing to its presumed degradation products acetic acid, ethyl acetate, methyl ethyl ketone and hydrogen peroxide. In the sense of an integrated testing strategy, further data on hydrolysis and confirmation of the hydrolysis products may inform the decision on whether a risk assessment for the oral route can rely on existing test data for the hydrolysis products. This approach would also be welcome in terms of animal welfare.*"

However, ECHA notes that there is no information in the dossier nor provided by the third party that supports third party's claim of such a rapid hydrolysis of the substance after oral ingestion and the formation of these supposed degradation products. ECHA acknowledge the third party comment but in the absence of scientific data supporting its claim, ECHA considers that there are no sufficient arguments to reject the test proposed by the Registrant.

Furthermore, the same third party indicates a reference to two repeated dose toxicity studies by dermal application in rats and mice. However, these studies are already present in the registration dossier and the Registrant considered them as not reliable since "*none of those studies are suitable for risk assessment of systemic toxicity after dermal contact, as severe local tissue (skin) damage was noted due to methyl-ethyl ketone peroxide`s corrosively*". ECHA notes that for both studies no OECD or EU guideline was followed and, due to the corrosive property of the substance, no NOAELs for local and systemic effects could be deduced. Hence, ECHA agrees with the Registrant's conclusion to consider these studies as not reliable and insufficient for fulfilling the information requirements of Annex IX, Section 8.6.2. of the REACH Regulation.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the registered substance.

2. Pre-natal developmental toxicity study

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD 414.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant did not specify the species to be used for testing and the route of administration. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used. Moreover, in accordance with paragraph 3 of Annex IX, *in vivo* testing with corrosive substances at concentration/dose level causing corrosivity shall be avoided and prior testing further guidance on testing strategies should be consulted in order to choose correct dosing level.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party suggested that "*On the basis of information presented in the Registration Dossier, the substance is expected to be readily hydrolysed after oral ingestion. The substance may therefore undergo immediate disintegration and not reach the blood without hydrolysing to its presumed degradation products acetic acid, ethyl acetate, methyl ethyl ketone and hydrogen peroxide. In the sense of an integrated testing strategy, further data on hydrolysis and confirmation of the hydrolysis products may inform the decision on whether a risk assessment for the oral route can rely on existing test data for the hydrolysis products. This approach would also be welcome in terms of animal welfare.*"

However, ECHA notes that there is no information in the dossier nor provided by the third party that supports third party's claim of such a rapid hydrolysis of the substance after oral ingestion and the formation of these supposed degradation products. ECHA acknowledge the third party comment but in the absence of scientific data supporting its claim, ECHA considers that there are no sufficient arguments to reject the test proposed by the Registrant.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance.

d) Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, Section 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that the conditions for adaptations are not fulfilled, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that the conditions for these adaptations can be fulfilled, he should update his technical dossier by clearly stating the reasons for proposing to adapt the standard information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal.

In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Moreover there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed. Specifically, the Registrant shall provide information on the concentration of the peroxide constituents and the type and concentration of stabilizers present in the sample tested.

Furthermore, the Registrant shall use a test material with the highest concentration of peroxide components technically achievable to avoid an underestimation of the hazardous properties of the registered substance, as explained in the introduction of Section III above.

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

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

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 or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. 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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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