ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114310471-65-01/F Helsinki, 11 December 2015

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

For Reaction mass of hydrogenated and dehydrogenated rosin, EC No 911-238-8, 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 jointly submitted registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for Reaction mass of hydrogenated and dehydrogenated rosin, hereinafter referred to as "the substance subject to this decision", submitted originally by [redacted] (the previous lead Registrant). The testing proposed can be summarized as follows:

- Pre-natal developmental toxicity study (OECD Guideline 414, rat, oral route) to be performed on Rosin (CAS No. 8050-09-7), and
- Two-generation reproduction toxicity study (OECD Guideline 416, rat, oral) to be performed on Rosin (CAS No. 8050-09-7).

This decision is based on the registration dossier as submitted with submission number [redacted]. In order to follow the procedure outlined in Articles 50(1) and 51 of the REACH Regulation and to allow ECHA to complete the necessary administrative practices for the Member States Competent Authorities' referral, ECHA took into consideration dossier updates pertinent to the decision received by the deadline of 7 January 2014 as agreed between ECHA and the Registrant. Additionally ECHA took into account dossier update caused by the transfer of the lead registrant role during the current decision making.

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.

On 27 September 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposal set out by the Registrant in the registration dossier for the substance mentioned above in relation to the testing proposals based on a read-across argumentation.

ECHA held a third party consultation for the testing proposals from 15 March 2011 until 29 April 2011. ECHA did receive information from third parties (see section III. below). The dossier was later updated by the Registrant with an additional testing proposal on two-generation reproductive toxicity.

On 29 April 2013, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the updated registration dossier.

ECHA held a third party consultation for the testing proposal from 19 July 2013 until 2 September 2013. ECHA did not receive information from third parties.

On 28 October 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 26 November 2013 ECHA received comments from the Registrant on the draft decision. On 17 December 2013 the Registrant updated his registration dossier (submission number [redacted]). ECHA considered the Registrant's comments and update. On basis of the comments, Section II (testing required) was not amended but the Registrant's comments are reflected in the Statement of Reasons (Section III) .

On 6 March 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.

Subsequently, proposals for amendment to the draft decision were submitted.

On 10 April 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 32 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and did not amend the draft decision.

On 22 April 2014 ECHA referred the draft decision to the Member State Committee.

By 12 May 2014, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposals for amendment into account.

A unanimous agreement of the Member State Committee on the draft decision relating to Pre-natal development toxicity study was reached on 26 May 2014 in a written procedure launched on 15 May 2014. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

On 13 June 2014, the previous lead Registrant, [redacted] informed ECHA that it has ceased the manufacture of the substance subject to this decision and indicated its willingness to step down from the lead registrant role. In the course of subsequent months the lead registrant role has been successfully transferred and accepted by [redacted], now addressee of the decision.

The present decision relates solely to the examination of the testing proposal for a Pre-natal developmental toxicity study. The testing proposal for Two generation reproductive toxicity study is terminated, as following the cease of manufacture of the previous lead registrant (the tonnage band of 1000 tonnes or more per year) and the current tonnage in the joint submission (tonnage band 100-1000 tonnes per year), this test is no longer applicable.

II. Testing required

The Registrant shall carry out the following test pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test method and the substance subject to the present decision:

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

while the originally proposed test for Pre-natal developmental toxicity study (test method: EU B.31/OECD 414) proposed to be carried out using a suggested analogue substance Rosin, CAS 8050-09-7, is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by [exact date – *12 months from the date of the decision* 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.

III. Statement of reasons

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

In relation to the testing proposal subject to the present decision, the Registrant has proposed to use a read-across approach, in accordance with Annex XI, 1.5, and to perform the proposed test on an analogue substance. ECHA has considered first the scientific validity of the proposed read-across approach (preliminary considerations; Section 0, below), before assessing the testing proposed (Section 1 below).

0. Read-across approach (preliminary considerations)

The evaluation by ECHA of testing proposals submitted by registrants aims at ensuring that generation of information is tailored to real information needs. To this end, it is necessary to consider whether programmes of testing proposed by Registrants are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards.

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), "provided that the conditions set out in Annex XI are met".

According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group such that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation.

The first Recital and the first Article of the REACH Regulation establish the "promotion of alternative methods for assessment of hazards of substances" as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to this decision by using the results of the proposed tests is sufficiently plausible based on the information currently available.

In that respect, the Registrant has submitted testing proposals, based on a read-across approach with Rosin (CAS No. 8050-09-7), in order to fulfil information requirements for pre-natal developmental toxicity (Annexes IX and X, 8.7.2.). More specifically, according to the Registrant, Rosin is a naturally occurring UVCB substance derived from wood. Rosin, regardless of its source, is used as a starting material for most commercially available derivatives, including Reaction mass of hydrogenated and dehydrogenated rosin (isomerised Rosin) as a typical derivative.

However, ECHA notes the reference substance, i.e. Rosin, is structurally significantly dissimilar to the substance subject to the present decision because the manufacturing process of the substance subject to the present decision (isomerisation of the Rosin) leads to hydrogen transfer between resins acids. More specifically, the unsaturated links in the molecules are hydrogenated in some cases and in others the unsaturation becomes aromatic moeties.

- In relation to structural similarity

In his comments to the draft decision and in the dossier update, the Registrant has provided further information on the chemical and structural similarity between Reaction mass of hydrogenated and dehydrogenated rosin (EC No 911-238-8), i.e. the substance subject to the present decision and the source substance of the read-across, i.e. Rosin (CAS No. 8050-09-7). According to the update, the substance subject to this decision contains 52,9% of dehydroabietic acid, whereas Rosin contains 17,4% of that constituent. Dehydroabietic acid is a form of resin acid, in which the conjugated diene structure has been converted to an aromatic ring by removal of hydrogen.

The Registrant considers that "the content of dehydroabietic acid and dihydroabietic acid is relatively high as the process used in creating the reaction mass removes reactive diene structures. A similar conversion can occur naturally. An aromatic ring (in the dehydroabietic acid) is well known to be more stable (less reactive) than aliphatic diene or triene structures. It is also a structure that may be formed during storage of pine chips prior to preparation of rosin. Thus it can be anticipated that the reaction mass will be less active chemically and biologically than the starting material, but within the range of activity describable for rosin." The natural conversion and low reactivity of this constituent have not been sufficiently documented.

Furthermore, the Registrant did not sufficiently establish chemical and structural similarity based on any of the options given in Annex XI. In particular, ECHA emphasizes the relevance of the "common breakdown products" referred to in Annex XI, 1.5. It has not been excluded that dehydroabietic acid will break down to metabolites, in which the aromatic component will be biologically active. This would have a significant impact on the toxicity of the substance. Therefore, information on the breakdown products and metabolism of rosins in general and that of dehydroabietic acid in particular are important in

regard of understanding whether a more reactive metabolite containing the aromatic ring is generated by metabolism. Relevance of the information on the breakdown products is pointed out in Annex XI, 1.5. of the REACH Regulation, which stresses that similarities between substances may be based on "the likelihood of common breakdown products via physical or biological processes, which results in structurally similar chemicals". There is no relevant toxicokinetic information in the updated dossier on any of the three members of this category of isomerised rosins.

ECHA also notes that Rosin is structurally significantly dissimilar to the substance subject to the present decision because the manufacturing process of the isomerized Rosin leads to hydrogen transfer between resins acids. More specifically, the unsaturated links in the molecules are hydrogenated in some cases and in others the unsaturation becomes aromatic moeties.

After evaluation of the comment of the Registrant and the dossier update, ECHA concludes that the Registrant has not provided sufficient information, which would substantiate the chemical and structural similarity of the substance subject to the present decision and the source substance of read-across, rosin.

- In relation to toxicity

In its update of the dossier, the Registrant has also provided a comparison of some basic ecotoxicity and toxicity properties of the substance subject to the present decision and Rosin. While this comparison provides limited support of similarity of the two substances it is noteworthy that comparison of repeated dose toxicity and reproductive toxicity is not possible, because there is no data available on these endpoints for both substances.

In particular, the sub-acute toxicity studies and the screening studies on reproductive and developmental toxicity, which could be used for justifying the toxicological similarity of the source and target substance of the read-across, are not available for both substances, which makes it impossible to compare these two substances for these endpoints. However, information on these endpoints are required at the tonnage of this registration.

In the update, the registrant also considers that "Disproportionated rosin may contain more than 50 weight-% of dehydroabietic acid, an aromatic ring containing molecule (see figure below). Taking this into account, it is doubtful that disproportionated rosin would pass the sameness test with rosin. Question is whether it would be acceptable to cross read from rosin to disproportionated rosin. The presence of an aromatic ring may trigger (eco) toxicologists to closer investigate whether disproportionated rosin can be included in this family." This statement implies that the Registrant has recognised the uncertainty on the toxicological similarity, but has not addressed it.

Furthermore, the Registrant has not provided a testing plan that would allow him to consider the validity of the read-across approach before deciding on conduction of the pre-natal developmental toxicity test (OECD 414).

ECHA therefore notes that the read-across hypothesis proposed by the registrant between substance subject to the present decision and Rosin, concerning pre-natal developmental toxicity is not sufficiently justified from the toxicological point of view.

- **Conclusion**

In conclusion, ECHA notes that several deficiencies remain in the read-cross hypothesis proposed by the Registrant.

The content of dehydroabietic acid, which contains the aromatic ring, is significantly higher in the substance subject to the present decision than in the proposed source substance of the read-across, i.e. Rosin.

Furthermore, the available data does not allow the comparison repeated dose systemic toxicity of these two substances and there is no information on the metabolism, i.e. break-down products of the substance subject to the presented decision.

Moreover, the Registrant has not proposed any testing plan that would allow him to assess the validity of the proposed read-across before the testing of the source substance commences. Although the Registrant has recognised the need "to closer investigate whether disproportionated rosin can be included in this family", he has not substantiated the read-across hypothesis with any strategy to develop experimental data.

It is ECHA's understanding that the difference in composition of Rosin and the substance subject to this decision may be associated with different hazardous properties between these two substances. Based on the above, the read-across hypothesis proposed by the Registrant does not satisfy several requirements of Annex XI, 1.5 and therefore is not considered plausible for the substance subject t to the present decision.

1. Pre-natal developmental toxicity study

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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, based on grouping of substances and read-across, for Pre-natal developmental toxicity study (OECD Guideline 414), proposed to be carried out, in rats, via the oral route with a suggested analogue substance (Rosin CAS No. 8050-09-7).

The Registrant proposed testing in rats by the oral route. 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.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

A third party suggests that before a Prenatal Developmental Toxicity Study (OECD Guideline 414), is conducted, consideration should be given to 1) the results of the existing 28- and 90-Day Sub-chronic Toxicity Studies and other toxicological data, 2) in vitro (pre-) validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity, and 3) exposure considerations: use the TTC for repeated dose and reproduction toxicity end points.

ECHA points out that the results of the repeated dose toxicity studies cannot be used to meet the information requirement for developmental toxicity. Secondly, the results of any currently available in vitro studies are not expected to meet the information requirement and due to the limited data bases (training sets) of the QSAR modes, it is unlikely that their results would be sufficient to meet the information requirement. Thirdly, from the data provided it can be preliminary concluded that the human exposure is low. However, since there is multitude of uses of rosin and rosin based products, including also consumer uses/applications, it cannot be claimed that "there is no or no significant human exposure". It is also noteworthy that the Registrant has not claimed that application of TTC concept could replace the relevant testing in this specific case.

Therefore, due to the reasons explained above, the information provided by third parties is not sufficient to fulfill this information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the substance subject to the present decision, while the originally proposed test for Pre-natal developmental toxicity study (test method: EU B.31/OECD 414) to be carried out using Rosin (CAS No. 8050-09-7) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

(e) Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation reproductive toxicity study (Annex X, 8.7.3.). As this endpoint is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is **19 December 2016.** The decision was therefore modified accordingly.

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. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed test, the sample of substance used for the new study 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 test 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 study 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.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the study to be assessed.

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.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.