EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000004855-65-05/F Helsinki, 14 August 2014

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

For Resin acids and Rosin acids, esters with pentaerythritol, CAS No. 8050-26-8 (EC No. 232-479-9), 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 Resin acids and Rosin acids, esters with pentaerythritol, CAS No 8050-26-8 (EC No 232-479-9), submitted by [redacted] (Registrant). The dossier contains a document "*Testing strategy for a UVCB category comprising Rosin Esters*", which can be summarised as follows:

- Sub-chronic toxicity (90-days) studies (OECD Guideline 408, rat, oral route) to be performed on Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7); and an additional sub-chronic toxicity study will be conducted on Esters of rosin oligomers with pentaerythritol (CAS No. 65997-12-8) if this substance is absorbed and demonstrates potential to cause systemic toxicity in an OECD 422 study.

- Pre-natal developmental toxicity study (OECD Guideline 414, rat, oral route) to be performed Resin acids and Rosin acids, methyl esters (CAS No. 68186-14-1); Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7); Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5); and Resin acids and Rosin acids, esters with pentaerythriol (CAS No. 8050-26-8; *i.e.* the substance subject to the present decision).

- Two-generation reproduction toxicity study (OECD Guideline 416, rat, oral), on Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7); Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5); and an additional two-generation reproduction toxicity study will be conducted on Resin acids and Rosin acids, esters with pentaerythritol (CAS No. 8050-26-8) if the absorption/hydrolysis studies on this substance indicate a potential for systemic toxicity exposure or if "*significant effects on the foetus*" are observed in either of the two-generation reproduction toxicity studies proposed above.

The present decision relates solely to the examination of the testing proposals for Sub-chronic toxicity (90-day) and Pre-natal developmental studies. The testing proposal for the

Two-generation reproductive toxicity study is addressed in a separate decision although the testing proposals were initially addressed together in the same draft decision.

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. In order to follow the procedure outlined in Articles 50(1) and 51 of the REACH Regulation and to allow ECHA 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

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 1 October 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 pre-natal developmental toxicity based on a read-across argumentation.

ECHA held a third party consultation for the testing proposal from 6 March 2012 until 20 April 2012. ECHA did receive information from third parties (see section III below).

The dossier was later updated by the Registrant with additional testing proposals for sub-chronic toxicity (90-days) and two-generation reproductive toxicity and additional substances covered by the category.

ECHA held a third party consultation for the testing proposals from 2 July until 26 August 2013. ECHA did receive information from third parties (see section III below).

On 21 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 20 November 2013 ECHA received comments from the Registrant on the draft decision.

On 20 December 2013 the Registrant updated his registration dossier (submission number [redacted]). In the updated registration dossier the Registrant substantially changed the category and read-across approach. In particular, the substances proposed to be tested as well as the number of proposed tests for each of the endpoints were changed.

The ECHA Secretariat considered the Registrant's comments and update. On basis of this information, Section II (testing required) was amended. The Statement of Reasons (Section III) was changed accordingly.

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 30 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 the Sub-chronic toxicity (90-days) and Pre-natal development toxicity studies 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.

II. Testing required

The Registrant has requested to carry out one of the two required tests using the substance subject to the present decision as part of a read-across and grouping approach, in accordance with Annex XI, 1.5., with respect to fulfilling the endpoint of Annex IX, 8.7.2. (pre-natal developmental toxicity).

The Registrant has requested to carry out the other of the two required tests using analogue substances as part of a read-across and grouping approach, in accordance with Annex XI, 1.5. with respect to fulfilling the endpoints of Annex IX, 8.6.2. (sub-chronic toxicity study, 90-days).ECHA emphasises that any final determination on the validity of the read-across, including the grouping approach proposed by the Registrant would be premature at this point in time. The eventual validity of the read-across hypothesis and grouping approach will be reassessed once the requested information from studies is submitted. Nevertheless, based on the information currently submitted, ECHA considers that the approach proposed by the Registrant is plausible.

In the light of this assessment ECHA has taken the following decision:

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 substances indicated below:

1. Sub-chronic toxicity study (90-days) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408) to be carried out using the analogue substances Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7); and, additionally, on Esters of rosin oligomers with pentaerythritol (CAS No. 65997-12-8) if this substance is absorbed and demonstrates potential to cause systemic toxicity in an OECD 422 study; and

2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414) to be carried out using the substance subject to the present decision, *i.e.* Resin acids and Rosin acids, esters with pentaerythriol (CAS No. 8050-26-8).

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.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfil this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

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.

3. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **21 August 2017** an update of the registration dossier containing the information required by this decision. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

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

The Registrant has requested to carry out the proposed tests using the substance subject to this decision (for pre-natal developmental toxicity) or analogue substances that are members of the same category (for sub-chronic toxicity) as part of a read-across and grouping approach, in accordance with Annex XI, 1.5. Accordingly, with respect to pre-natal developmental toxicity, ECHA has considered that as the testing is proposed with the substance subject to the present decision considerations on the grouping of substances and read-across do not apply to the present decision. Such considerations and ECHA conclusions are provided in respective draft decisions on the substances that are members of the category. For sub-chronic toxicity and, ECHA has considered first the scientific validity of the proposed read-across and grouping approach (preliminary considerations; Section 0, below), before assessing the testing proposed (Sections 1, below).

0. Grouping of substances and read-across approach (preliminary considerations)

0.1. Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis brought forward by the Registrant

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 Registrant has submitted testing proposals, based on a grouping and read-across approach, intended to fulfil information requirements for sub-chronic toxicity (90-days; Annex IX, Section 8.6.2.).

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.

0.2. Grouping of substances and read-across hypothesis as proposed by the Registrant

According to the Registrant, the substance subject to this decision can be grouped with other substances in a category for the purpose of read-across. The grouping is based on the presumption that all substances that are members of the category are structurally related, *i.e.* all the substances are UVCBs (substances of Unknown or Variable composition, Complex reaction products or Biological materials) derived from the UVCB starting material Rosin CAS No. 8050-09-7 (EC No. 232-475-7) which may be subjected to hydrogenation or oligomerisation prior to esterification.

The Registrant considers "*The alcohol used in the esterification process influences both the 3-D structure and molecular weight of the products that are formed, and supports informal differentiation of the category members into simple, linear and bulky esters. The former appear potentially susceptible to enzyme breakdown with possible release of the parent reactants, while steric hindrance may lead to internalization of ester bonds in the latter suggesting they may resist enzymatic attack; the linear esters appear intermediate. Their chemical and biological properties may therefore vary in a regular and predictable manner that reflects the underlying structural features present.*"

According to the Registrant, the "*members of this category are formed by the esterification of rosin with methanol, mono-, di- or triethyleneglycol, glycerol and pentaerythritol*" and that "*they are composed primarily of esterified resin acids, with non-esterified acids generally accounting for less than* [redacted]*% of the total*".

In ECHA's understanding, the Registrant's read-across hypothesis is that the toxicity of the substances within the category will decrease with increasing complexity of the ester formed. The Registrant hypothesises that smaller esters will be more toxic than the larger esters within the category, that the toxicity observed in the category is expected to be that of the starting material, and that accurate predictions of the toxicological properties within the category can be made if *ex vivo* absorption and *in vitro* enzymatic hydrolysis studies are considered together with the available/proposed toxicological studies.

0.3. Information submitted by the Registrant to support the grouping of substances and read-across hypothesis

The Registrant has provided a justification document for the category of '*Rosin esters*'. This document contains, criteria for category membership, a list of category members, an overview grouping of substances and approach proposed; additional information on the testing proposals for sub-chronic toxicity (90-days) and pre-natal developmental toxicity, including a rationale for selection of test material(s); a summary of the composition ranges and physico-chemical properties of the category members; information on the underlying chemistry; and an overview of planned/on-going experimental work (*ex vivo* absorption tests, *in vitro* enzymatic hydrolysis studies and combined repeated dose toxicity study with the reproduction/developmental toxicity screening tests, OECD Guideline 422) intended to increase the scientific confidence in the category.

With regard to sub-chronic toxicity, the Registrant has provided information from feeding studies in rats on four substances in the category which is summarised as follows: For Resin acids and Rosin acids, hydrogenated, Me esters (CAS No. 8050-15-5) two sub-chronic toxicity studies have been provided which both report a NOAEL 500 ppm in males/females, in addition the Registrant has performed benchmark dose modelling of these studies and this analysis provides a $BMDL_{10\%}$ of 152 mg/kg body weight/day in males/females based on hepatocyte hypertrophy; for Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5) three sub-chronic toxicity studies have been provided, the first study reports a NOAEL for systemic toxicity at 10000 ppm (equivalent to about 714/815 mg/kg body weight/day) in males/females, the second study reports a NOAEL for systemic toxicity at 10000 ppm in males/females, and the third study reports a NOAEL for systemic toxicity at 2500 mg/kg body weight/day in males/females; for Resin acids and Rosin acids, hydrogenated, esters with glycerol (CAS No. 65997-13-9) study reports a NOAEL for systemic toxicity at 10000 ppm males/females; and for Resin acids and Rosin acids, hydrogenated, esters with pentaerythritol (CAS No. 64365-17-9) the study reports a NOAEL of 10000 ppm in feed. ECHA further notes that sub-chronic systemic toxicity was observed in the low molecular weight ester Resin acids and Rosin acids, hydrogenated, Me esters (CAS No. 8050-15-5), whereas the studies conducted on higher molecular weight esters did not show systemic toxicity below 10000 ppm in the diet.

With regard to reproductive/developmental toxicity screening tests (OECD Guideline 421 or 422), the Registrant has provided feeding studies in rats on two substances in the category. For Resin acids and Rosin acids, esters with pentaerythritol (CAS No. 8050-26-8) the OECD 421 study reports a NOAEL of 20000 ppm in males/females for reproductive and developmental effects; and Resin acids and Rosin acids, hydrogenated, Me esters (CAS No. 8050-15-5) the OECD 422 study reports a NOAEL for parental sub-acute toxicity of less

than 5000 ppm (approximately <405/<476 mg/kg body weight/day) in males/females, a NOAEL for reproductive effects of 20000 ppm in males and 10000 ppm in females, and a NOAEL for developmental effects of 5000 ppm. ECHA notes that sub-acute systemic toxicity and developmental effects were observed in the low molecular weight ester Rosin acids, hydrogenated, Me esters (CAS No. 8050-15-5).

In addition, the Registrant commits in the testing programme to conduct *ex vivo* absorption tests on all category members, *in vitro* enzymatic hydrolysis studies on representative members of the category, and combined repeated dose toxicity study with the reproduction/developmental toxicity screening tests (OECD Guideline 422) on Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); Resin acids and Rosin acids, esters with diethylene glycol (CAS No. 68153-38-8); Resin acids and Rosin acids, hydrogenated, esters with triethylene glycol (CAS No. 68648-53-3); and Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5). The Registrant is intending to conduct an additional OECD 422 study on Esters of rosin oligomers with pentaerythritol (CAS No. 65997-12-8) if the *ex vivo* absorption study on this substance indicate a potential for absorption.

The Registrant intends to use the information obtained from the *ex vivo* absorption studies as a quantitative indication of uptake and as a qualitative assessment of which chemical species are absorbed. The *in vitro* enzymatic hydrolysis, the *ex vivo* absorption, and OECD 422 studies are intended by the Registrant to support the read-across hypothesis and provide information to what extent the toxicological properties vary within the category.

0.4. ECHA analysis of the selection of substances to be tested

The Registrant hypothesises that there is a trend of toxicity within the category for the relevant endpoints; *i.e.* the toxicity decrease with increasing complexity of the ester formed. According to the Registrant, the structural variation within the category is caused by the fact that the starting material Rosin; Rosin, hydrogenated; or Rosin, oligomers is esterified. Depending on which alcohol that is used for the esterification the resulting ester will be "*simple*" (*i.e.* methanol ester), "*linear*" (*i.e.* mono-, di- or tri-ethyleneglycol esters), or "*bulky*" (*i.e.* glycerol or pentaerythritol esters).

ECHA has considered each substance proposed to be tested in the light of this assumed trend, available toxicological information within the category, and major ester types in the substances proposed to be tested.

For sub-chronic toxicity (90-days), the Registrant has already submitted a sub-chronic toxicity study on the "*simple*" ester Resin acids and Rosin acids, hydrogenated, Me esters (CAS No. 8050-15-5) in which systemic toxicity was observed (reported NOAEL 500 ppm in the diet), and sub-chronic toxicity studies on three "*bulky*" esters where the reported NOAELs where 10000 ppm or greater in the diet. The Registrant has proposed to test two substances for sub-chronic toxicity (90-days):

i. Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2) which is the smallest of the "*linear*" esters and this substance consists of up to [redacted]% mono- and up to [redacted]% di-esters; and
ii. Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7) which is the largest of the "*linear*" esters and this substance consists of up to [redacted]% di-esters.

In addition, a sub-chronic toxicity study will be conducted on Esters of rosin oligomers with pentaerythritol (CAS No. 65997-12-8) if this substance is absorbed and demonstrates

potential to cause systemic toxicity in an OECD 422 study; this substance represents the upper boundary of the category.

ECHA notes that the two "*linear*" esters proposed to be tested will provide new information that may allow the Registrant to fill the gap in the assumed trend between "*simple*" esters and "b*ulky*" esters. Furthermore, the study on Esters of rosin oligomers with pentaerythritol may – if triggered – be used to confirm the assumed trend in toxicity within the category.

0.5. ECHA analysis of the grouping approach and the read-across hypothesis of the Registrant in light of the requirements of Annex XI, 1.5

ECHA understands that the grouping approach is based on a structural similarity resulting from the common UVCB starting material Rosin (which may be subjected to hydrogenation or oligomerisation prior to esterification) and that the members of this category are formed by the esterification of the starting material with methanol, mono-, di- or triethyleneglycol, glycerol and pentaerythritol. Because the Registrant considers the compositional diversity within the category will vary in a predictable manner he further considers that the grouping is suitable for the purpose of read-across. ECHA has analysed the grouping approach proposed by the Registrant and considers that the criteria and the boundaries of the category have been sufficiently defined.

ECHA understands that the read-across hypothesis assumes that the chemical and biological properties of substances within the category will vary in a regular and predictable manner that reflects the underlying structural features present. Specifically, the Registrant recognises that the alcohol used in the esterification process influences the 3-D structure and molecular weight of the products that are formed, that some of the substances may be susceptible to enzymatic breakdown with possible release of the parent reactants, and that due to steric hindrance of ester bonds some substances may resist enzymatic attack.

Based on the currently limited toxicological information, information on composition and supporting information about the underlying chemistry of the category members, ECHA considers the read-across approach plausible with respect to sub-chronic toxicity and two-generation reproduction toxicity. However, the limited toxicological information currently available does not allow reaching a conclusion on the assumption of a trend for all substances within the category. This circumstance creates uncertainties that will have to be addressed by the Registrants in order to meet the condition set out in Annex XI, Section 1.5. of the REACH Regulation.

The Registrant has recognised the necessity to provide sufficient toxicological information to substantiate the hypothesis for the substances in the category and committed to undertake additional studies intended to strengthen the toxicological information for the read-across approach. This includes combined repeated dose toxicity studies with the reproduction/ developmental toxicity screening tests on Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); Resin acids and Rosin acids, esters with diethylene glycol (CAS No. 68153-38-8); Resin acids and Rosin acids, hydrogenated, esters with triethylene glycol (CAS No. 68648-53-3); and Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5). An additional OECD 422 study on Esters of rosin oligomers with pentaerythritol (CAS No. 65997-12-8) will be conducted if the *ex vivo* absorption study on this substance indicate potential for gastrointestinal absorption. ECHA considers that generating this additional information is therefore an essential condition for the ultimate acceptance and use of read-across for the category.

The Registrant has committed to provide *ex vivo* absorption data on all members of the category. Absorption information is to be generated using an "everted gut-sac model". ECHA considers that this model is currently not validated for this type of substances, and that the Registrant has not demonstrated that the *ex vivo* absorption observed accurately predicts *in vivo* gastrointestinal absorption and ultimately correlates to the systemic toxicity observed in available toxicity studies. These uncertainties will have to be addressed by the Registrant. Nevertheless, ECHA considers that information on bioavailability is useful to strengthen the read-across argumentation and considers it to be an essential condition for the ultimate acceptance and use of read-across for the category.

Moreover, the Registrant has committed to conduct *in vitro* enzymatic hydrolysis studies on representative members of each of the three different ester classes within the category *i.e.* '*simple*', '*linear*' and '*bulky*' esters, and possibly later expand it to all category members. ECHA considers that this model is currently not validated for this type of substances, that the Registrant has not demonstrated that the *in vitro* enzymatic hydrolysis observed accurately predicts *in vivo* hydrolysis in the gastrointestinal tract, and that the rate of *in vitro* hydrolysis correlates to the rate of absorption of the hydrolysis products and ultimately correlates to the systemic toxicity observed in available toxicity studies. These uncertainties will have to be addressed by the Registrant. Nevertheless, ECHA considers that information on *in vitro* enzymatic hydrolysis is useful to strengthen the read-across argumentation and considers it to be an essential condition for the ultimate acceptance and use of read-across for the category.

The Registrant has proposed to test two substances for sub-chronic toxicity taking into account the structural variability and available sub-chronic toxicity studies within the category. ECHA considers that the substances proposed for testing may allow the Registrant to:

i. conclude on a trend for sub-chronic toxicity within the category;

and that the grouping may ultimately, if the assumptions are confirmed, be acceptable for ECHA.

In the case where the result of the proposed studies performed in accordance with the present decision would not confirm the grouping and read-across hypothesis relied upon by the Registrant, this outcome shall not alter the obligation of the Registrant to meet the standard information requirements. Should the read-across strategy be inadequate, it is the responsibility of the Registrant to ultimately submit reliable information or adaptations which is used in a way that does not underestimate hazards of the registered substance in relation to the relevant endpoints.

Finally, the read-across adaptation based on the results of the proposed tests shall ensure that any remaining uncertainties, including results of any existing studies which might give rise to concern, are analysed, minimized, and taken into account for the purpose of classification and labelling and/or risk assessment.

In any case, following the update of the dossier submitting the information required in the present decision, ECHA will determine whether the documentation provided is sufficient to satisfactorily address the information requirement of Annex IX for the substance subject to the present decision.

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

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. The information on this endpoint is not available for the substance subject to this decision. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes that the Registrant has submitted oral sub-chronic toxicity studies (90-days; OECD Guideline 408) on the substances Resin acids and Rosin acids, hydrogenated, Me esters (CAS No. 8050-15-5); Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5); Resin acids and Rosin acids, hydrogenated, esters with glycerol (CAS No. 65997-13-9); and Resin acids and Rosin acids, hydrogenated, esters with pentaerythritol (CAS No. 64365-17-9). ECHA concludes that the sub-chronic toxicity studies already submitted by the Registrant are not sufficient on their own to fulfil the information requirement for sub-chronic toxicity (90-days) according to Section 1.5 of Annex XI of the REACH Regulation for the substance subject to the present decision.

In addition, the Registrant has submitted a testing proposal, based on grouping of substances and read-across, for sub-chronic toxicity studies (90-days; EU B.26/OECD 408) proposed to be carried out in rats via the oral route with the substances Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7); and an additional sub-chronic toxicity study will be conducted on Esters of rosin oligomers with pentaerythritol (CAS No. 65997-12-8) if this substance demonstrates potential to cause systemic toxicity in the on-going OECD 422 study.

Based on ECHA's preliminary considerations on the grouping of substances and read-across approach (see Section 0, above) ECHA considers that the approach proposed is plausible.

The Registrant proposed testing by the oral route. In the light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is appropriate.

b) Consideration of the information received during third party consultation

ECHA did not receive third party information concerning the testing proposal on this endpoint during the third party consultation.

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 analogue substances Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); and Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7); and, additionally, on Esters of rosin oligomers with pentaerythritol (CAS No. 65997-12-8) if this substance is absorbed and demonstrates potential to cause systemic toxicity in an OECD 422 study.

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 two oral reproduction/developmental toxicity screening studies (OECD Guideline 421 or 422) on the substances Resin acids and Rosin acids, esters with pentaerythritol (CAS No. 8050-26-8); and Resin acids and Rosin acids, hydrogenated, Me esters (CAS No. 8050-15-5). ECHA notes that in the OECD 422 study performed using Rosin acids, hydrogenated, Me esters developmental effects were observed.

In addition, the Registrant has submitted a testing proposal, based on grouping of substances and read-across, for a pre-natal developmental toxicity study (EU B.31/OECD 414), proposed to be carried out, in rats, via the oral route with the substances Resin acids and Rosin acids, methyl esters (CAS No. 68186-14-1); Resin acids and Rosin acids, esters with ethylene glycol (CAS No. 68512-65-2); Resin acids and Rosin acids, esters with triethylene glycol (CAS No. 8050-25-7); Resin acids and Rosin acids, esters with glycerol (CAS No. 8050-31-5); and Resin acids and Rosin acids, esters with pentaerythriol (CAS No. 8050-26-8; *i.e.* the substance subject to the present decision).

While ECHA considers OECD Guideline 421/422 studies useful to screen substances for potential to cause reproduction/developmental toxicity, the tests are not sufficient to meet the information requirement for pre-natal developmental toxicity according to Section 8.7.2 of Annexes IX and X.

ECHA notes that one of the substances proposed to be tested is the substance subject to the present decision. Therefore, ECHA considers that for the purpose of this decision testing with the substance subject to the present decision is sufficient to fulfil the information requirements for pre-natal developmental toxicity.

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 refers to column 2 of Annex IX and X of Regulation (EC) No 1907/2006 according to which the study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*".

ECHA points out that while the existing data suggest that some 'rosin esters' may be of low toxicity; there is no sub-chronic repeated dose toxicity study performed with the registered substance. Therefore, the first criteria of Annex IX, 8.7, column 2 does not apply. ECHA points out that absence of data does not support a notion of no effects. Secondly, the available data on absorption suggests that the bioavailability is below 5%, and thus it can not be proved that no systemic absorption occurs. Furthermore, these toxicokinetic data have been obtained by using a substance other than the registered substance. 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 it can not be claimed that "*there is no or no significant human exposure*". It is also noteworthy that the Registrant has not claimed that these criteria of column 2 would apply to the registered substance.

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

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed 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.

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 pre-natal 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, 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, 8.7.2. of the REACH Regulation.

3. Deadline for submitting the required information

In the draft decision communicated to the Registrant, the deadline to provide the requested information was 36 months from the date of adoption of the decision. In his comments on the draft decision of 6 December 2013 the Registrant requested an extension of the timeline to 48 months.

The Registrant put forward several arguments. Firstly, he highlights the complexity of the testing strategy, which requires sequential testing for several endpoints and substances, and thereafter reassessment of the read-across and category approach in view of the results. Secondly, in order to minimise variability and facilitate interpretation of data for the category the Registrant intends to perform the tests in the same testing facility.

Considering the complexity of the overall testing strategy, number of tests to be performed and need for sequential testing, ECHA concluded that there are justified reasons to extend the deadline. Therefore, the deadline was extended to 48 months in the draft decision communicated to the Member State Competent Authorities. This deadline took into account the fact that the draft decision also requested a reproductive toxicity study (Annex X, 8.7.3). As the testing proposal for this study is not addressed in the present decision, ECHA considers that a reasonable time period for performing the remaining test(s) is 36 months from the date of the adoption of the decision. Therefore, ECHA changed the deadline from 48 months to 36 months.

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 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.

Finally 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.

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://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.

[redacted]
Leena Ylä-Mononen
Director of Evaluation