Decision number: CCH-D-2114288816-32-01/F Helsinki, 20 March 2015

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

For Reaction mass of L-xylo-hex-2-ulosonic acid and ascorbic acid (EC No 932-019-3), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for Reaction mass of L-xylo-hex-2-ulosonic acid and ascorbic acid, submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirement of Annex IX, Sections 8.6.2. and 8.7.2. of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

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

This decision is based on the registration 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 submitted after 12 June 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.

The compliance check was initiated on 7 March 2013.

On 31 May 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 27 June 2013 ECHA received comments from the Registrant on the draft decision.

On 24 September 2013 the Registrant updated his registration dossier with the submission number [redacted] The ECHA Secretariat considered the Registrant's comments and update. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 12 June 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 18 July 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 amended Section III of the draft decision.

On 28 July 2014 ECHA referred the draft decision to the Member State Committee.

By 18 August 2014 in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments on the proposals for amendment of the Registrant into account.

After discussion in the Member State Committee meeting on 16-18 September 2014, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 17 September 2014.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annex IX, of the REACH Regulation the Registrant shall submit the following information 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); 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).

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **27 March 2017**. The timeline has been set to allow for sequential testing as appropriate.

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 sound 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 Authorities of the Member States for enforcement.

Furthermore, 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. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2.

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

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirement.

The Registrant provided comments to the initial draft decision and updated the registration. In the updated registration dossier the Registrant sought to address the requirements for a 90-day sub-chronic toxicity study (Annex IX, 8.6.2.) and a pre-natal developmental toxicity study (Annex IX, 8.7.2.), by using data obtained with the substances D-glucono-1,5-lactone (further referred to as DGL; CAS No 90-80-2) and D-gluconic acid (further referred to as DGA; CAS No 526-95-4). A read-across justification document was provided as part of the comments to the initial draft decision and in the updated registration.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

The following analysis presents the Registrant's justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis of the justification in both a generic and an endpoint-specific context.

a. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

In the updated registration, the Registrant has provided study records for an OECD 422 screening study with the registered substance and for a 6 and 24 month oral toxicity study in rats both performed with the analogue substance DGL to cover the endpoint sub-chronic toxicity. To cover the endpoint pre-natal developmental toxicity, the Registrant has provided the OECD 422 screening study with the registered substance as well as several study records for pre-natal developmental toxicity studies in rats, mice, rabbits or hamster with the proposed analogue substance DGL.

ECHA understands from the read-across justification document that the read-across is based on similarity of the chemical structures of the two source substances DGL and DGA and the main component of the registered substance, *viz.*, [redacted]; represents about [redacted]% of the registered substance) and a perceived similarity of properties of the two sources (DGL and DGA) and [redacted]

resulting from structural similarity. Therefore, the main component, not the registered substance, is the target substance of the read-across performed by the Registrant.

The Registrant further assumes that the other components, which represent about [redacted]% of the registered substance, do not influence the considered toxicological endpoints. Thus the Registrant regards it justified to use the results obtained with the source substances to meet the information requirements for the complete registered substance.

b. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

The following arguments were provided by the Registrant to support the read-across. First the arguments based on structural similarity of DGL, DGA and [redacted] are presented, followed by the arguments for the absence of toxicity of the other components.

The Registrant's arguments for the read-across from the sources DGL, DGA to the target [redacted]:

1. The presence of a [redacted] instead of a hydroxyl group on the second C atom in DGL and DGA is "*considered minor in regards to the profiling as ketoacids undergo oxidative decarboxylation to yield carbon dioxide and their corresponding aliphatic acids. Therefore, once converted to the shorter acid, the metabolite will be metabolized completely in the fatty acid pathway or citric acid cycle.*"
2. A study of 1957 showed that after intraperitoneal administration only 1.2-1.4% of [redacted] was "*converted to* [redacted]*, with the majority excreted in the urine ...*" "*This is consistent with the differential metabolism observed in studies with gluconate salts in which intraperitoneal administration resulted in 60-85% of the administered dose being excreted in urine unchanged while oral studies in man demonstrate complete catabolism ...*". "*It is well established the DGA (or DGL) are substrates of normal glucose oxidation and it is expected that* [redacted] *would be expected to be metabolized per normal endogenous compounds; therefore, neither of these compounds indicates a differential concern.*"
3. The Registrant compares the results of an oral (gavage) "*repeated dose screening study on* [redacted] *in Sprague-Dawley rats*" with the results of repeated-dose studies with the two source substances. The results of the study with [redacted] are interpreted as to be "*mainly indicative of the acidic nature of the compound*". Also the effects observed in a gavage study with the sodium salt of DGA with rats are interpreted as to be the result of the acidic nature of the test compound. It is then stated: "*... this observation provides a comparative read across to the irritant nature of the compound and* [redacted] *and the lack of systemic findings.*" Further repeated-dose toxicity studies with DGA and DGL are concisely presented in the comments by the Registrant, all perceived to show hardly any systemic toxicity. Together the presentation of these data leads the Registrant to state the following. "*Based on structural similarities and the common duration studies and their findings, there exists clear reasoning for read-across of* [redacted] *to gluconic acid and derivatives class for longer duration repeated dose toxicity studies.*" "*In summary, these studies reiterate the lack of systemic effects from the surrogate compound and, as predicted,* [redacted]*.*"

4. The Registrant states: "*Further support for the lack of toxicity from the read across to this surrogate can be found by considering the data on other dicarboxylic acids with additional functional groups.*"
5. The Registrant states: "*..., the target chemical and the surrogate are both fairly simple structures, differing only slightly in MW, a fact that would impart no difference in toxicity. The only difference in these compounds is the target compound having a ketone moiety at carbon 2 versus a hydroxyl; however, this would not inhibit normal metabolism by well understood biochemical pathways (β-oxidation, TCA).*"
6. The Registrant states: "*Neither compound is expected to bind estrogen receptors.*"
7. The Registrant states: "[redacted] *is predicted to be 'NON-Toxicant' for developmental toxicity based on modelling in the Developmental Toxicity model CEASAR ..., with a similarity score of 0.965 to the potassium salt of DGA ... . As such, there is no information to suggest that* [redacted] *would interfere with developmental process and data support the read across argument for the gluconic acid group.*"
8. The Registrants compares the results of the OECD 422 study with [redacted] with a series of pre-natal developmental studies with DGL. Based on this comparison the following is concluded: "*Based on the structural similarities of the two compounds, as well as supporting information ... , read-across is justified for the* [redacted] *compound to the glucono-delta-lactone for the fulfillment of the developmental toxicity endpoint.*"
9. The Registrant states: "*The read across to developmental toxicity based on the large database on the surrogate is considered to have high confidence.*"

The Registrant's arguments for the absence of influence of the other components than [redacted] on the considered endpoints:

10. The other components than [redacted] include, as mentioned by the Registrant in the justification document, [redacted]. Various reasons are put forward to substantiate the lack of influence of these substances on the considered endpoints.

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

ECHA's assessment of the 10 arguments presented above:

Ad 1. ECHA finds that this argument does not support the read-across from the sources DGA and DGL to the [redacted]. The argument suggests a possible metabolic route of [redacted] and the ultimate sequestration of the compound via the citric acid cycle and/or fatty-acid metabolism.

It is noted by ECHA that in its view there is a possible influence of the hydroxylation of the alkyl chain on the anticipated [redacted] and on the further metabolism of the product of the anticipated decarboxylation, and that this is not addressed by the Registrant.
Moreover, ECHA notes that the study from 1957 (in point 2. above) does not support significant biotransformation of [redacted] to the contrary, it seems that when administered by the intraperitoneal route [redacted] is rather stable in the body of rats and guinea pigs, and largely excreted as such via the urine.

Ad 2. This argument is not justified because the Registrant has not demonstrated that his assumptions about the metabolism of [redacted] upon oral exposure are correct. The argument depends on the assumption that the difference in the extent of metabolism between the metabolism of DGA upon intraperitoneal administration and oral exposure also applies to [redacted]. Without information on the actual metabolism of [redacted] following oral exposure no support of such assumption is provided. In view of ECHA's assessment of the first argument, it is difficult to understand why *"neither of these compounds indicates differential concern"*. ECHA notes that in the comments on the proposals for amendment, the Registrant concludes that *"the available literature supports the position that* [redacted] *has limited oral absorption, with most of the orally administered material fermented in the large intestine. Any absorbed* [redacted] *would likely be excreted unmetabolized, though some fraction of the compound may be metabolized, following the route of decarboxylation or alcohol biotransformation with direct conjugation or oxidation by alcohol dehydrogenase to the corresponding aldehyde and carboxylic acid, which would be metabolized or excreted. This postulation is based on reviews of compounds with similar functional groups, including endogenous α-keto acids, as described in the original read across submission."*

ECHA notes that in the documentation provided by the Registrant on [redacted] *only 10% of the ingested* [redacted] *are eliminated by this way."* ECHA notes that this finding indicates uptake of [redacted] after oral administration. However, the documents provided are not suitable to draw any further conclusion whether [redacted] itself is metabolised. ECHA further notes that the metabolic pathway of [redacted] as proposed by the Registrant is based on expected metabolism of flavouring substances which may have similar functional groups but otherwise chemical structures that are quite different to that of [redacted].

Ad 3. One gavage sub-acute repeated-dose toxicity study with [redacted] is compared with a series of oral (gavage and feeding) *"common duration"* repeated-dose studies with the source substances. For a series of repeated-dose toxicity studies with DGA and DGL the Registrant did not report systemic toxicity and this combined with the results of a sub-acute repeated-dose toxicity study with [redacted] leads him to conclude that an sub-chronic repeated-dose toxicity study with [redacted] would yield the same effects as the studies with DGA and DGL. This comparison does not demonstrate as to why the read-across conclusion is justified.

Ad 4. ECHA notes that [redacted] is not a dicarboxylic acid.

Ad 5. The statement of the author is not substantiated by further data. Both, the expectation *"a fact that would impart no difference in toxicity"* and the expectation that *"this would not inhibit normal metabolism ..."* are thus regarded by ECHA as purely hypothetical. Moreover, the absence of inhibition of a normal metabolism of the target substance does not imply that the target substance has the same toxicological effects as the source substances.

Ad 6. A QSAR prediction that both substances will not bind to estrogen receptors does not preclude pre-natal developmental toxicity.

Ad 7. Based on the information provided by the Registrant, ECHA cannot judge the validity, applicability and reliability of the model in the present context.

Ad 8. The comparison made by the Registrant of the single OECD 422 study with the target substance with the evidence on the developmental toxicity of the source substances does not demonstrate as to why the read-across conclusion is justified.

Ad 9. The "*large database on the surrogate*" only provides information on the source substances and does in itself not substantiate the possibility to use those data to meet the information requirement for the registered substance including [redacted] as the main constituent.

Ad 10. ECHA considers that the Registrant has not fully justified and demonstrated that the other components, about [redacted]% of the registered substance, will not influence the proposed read-across. Without detailed information ECHA cannot indepently assess or conclude whether or not the approach is acceptable.

In addition, ECHA notes that this argument does not necessarily cover [redacted]. As regards this component of the registered substance, the Registrant states: "[redacted] *... is similar in structure to* [redacted] *and would be expected to have the same toxicological profile.*" ECHA cannot accept this statement as such, because the presence of the extra ketone group in such a small molecule can be regarded as a significant structural difference from [redacted] and the Registrant has not justified his opposite assumption. It can not *a priori* be concluded, therefore, that the two substances will have the same toxicological profile. ECHA further notes that in the comments on the proposals for amendment, the Registrant refers to existing information on [redacted] and [redacted]. ECHA further notes that the read-across approach from DGA/DGL to [redacted] failed for the reasons mentioned above and that the additional information provided in the comments to the proposals for amendment does not change that conclusion.

d. Conclusion on the read-across approach

The information, data and reasoning provided does not allow ECHA to accept the read-across from the source substances DGL and DGA to [redacted] and the registered substance.

ECHA concludes that the read-across approach is not adequately justified and documented. The Registrant has not provided sufficient information on metabolism of [redacted] after oral administration and how the metabolism of [redacted] is interlinked with the metabolism of DGA/DGL. Consequently, it has not been shown that the metabolic fates of the substances are likely to be similar and that the toxicological properties of the registered substance can be accurately predicted from DGL/DGA. In addition, ECHA considers that the Registrant has not fully justified and demonstrated that the other components, about [redacted]% of the registered substance, will not influence the proposed read-across. Without detailed information ECHA cannot independently assess or conclude whether or not the approach is acceptable.

Consequently, ECHA considers that the proposed read-across approach does not fulfil the requirements defined in Annex XI, 1.5. of likely similar toxicological properties based on common functional groups, common breakdown products and adequacy for the purpose of classification and labelling and/or risk assessment. As a result and based on the information

analysed by ECHA in the light of above deficiencies and based on the information provided, these substances cannot be used for read-across purposes.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements in the technical dossier, based on the read-across substances, does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5. Consequently, where an adaptation according to Annex XI, 1.5. has been presented by the Registrant, the information in the technical dossier is not sufficient to comply with the standard information requirements.

Irrespective of the unsuitability of the read across approach, ECHA has considered the read-across approach separately for each endpoint in which this approach has been applied.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

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. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier the Registrant provided information with which he sought to fulfil this standard information requirement. The provided information stems from a "Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422). However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days. The technical dossier neither contained a testing proposal nor an adaptation in accordance with column 2 of Annex IX, Section 8.6.2. or with the general rules of Annex XI for this standard information requirement.

In the comments to the initial draft decision and in an updated registration dossier, the Registrant has adapted the required information by read-across. ECHA has evaluated the Registrant's read-across approach and concluded that it does not fulfil the requirement defined in Annex XI, 1.5. (see Section III, 0. above).

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In light of the properties of the substance (liquid with low vapour pressure irritating to eyes) and the information provided on the uses and human exposure (i.a. no spray application), ECHA considers that testing by the oral route is most appropriate. According to the test method the rat is the preferred rodent species. ECHA considers this species as being appropriate.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit information on sub-chronic toxicity (90-day) in rats, oral route (test method EU B.26./OECD 408) derived with the registered substance subject to the present decision.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

A pre-natal developmental toxicity study is a standard information requirement as laid down in Annex IX, section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier the Registrant provided information with which he sought to fulfil this standard information requirement. The provided information stems from a "Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422). However, this study does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study like examination of fetuses for skeletal and visceral alterations. The technical dossier neither contained a testing proposal nor an adaptation in accordance with column 2 of Annex IX, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

In the comments to the initial draft decision and in an updated registration dossier, the Registrant has adapted the required information by read-across. ECHA has evaluated the Registrant's read-across approach and concluded that it does not fulfil the requirement defined in Annex XI, 1.5. (see Section III, 0. above).

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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.

Therefore, pursuant to Article 41(1) and 41(3) of the REACH Regulation, the Registrant is requested to submit information on Pre-natal developmental toxicity on rats or rabbits, oral route (test method EU B.31/OECD 414) on the registered substance.

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, 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.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. The Registrant is reminded of his responsibility to ensure that his registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In carrying out the studies required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, 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. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]

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