EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000004544-74-02/F Helsinki, 17 November 2014

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

For D-gluconic acid, CAS No 526-95-4 (EC No 208-401-4), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for D-gluconic acid, CAS No 526-95-4 (EC No 208-401-4), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirement of Annex VII, Section 8.4., and Annex VIII, Section 8.4. of the REACH Regulation.

This decision is based on the registration dossier as submitted with submission number [redacted] for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 3 January 2014, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 19 September 2012.

On 14 December 2012 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 11 January 2013 ECHA received comments from the Registrant.

On 19 June 2013 the Registrant updated his registration dossier (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 3 January 2014 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

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

II. Information required

Pursuant to Articles 41(1)(b), 41(3), 10(a)(vii), 12(1)(e), 13 and Annexes VII and VIII 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:

a. *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.; test method: EU B.13/14/OECD 471);
b. *In vitro* cytogenicity study in mammalian cells (Annex VIII, 8.4.2., test method: EU B.10/OECD 473) or *in vitro* micronucleus study (Annex VIII, 8.4.2.; test method: OECD 487);
c. *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.; test method: EU B.17/OECD 476), provided that there is a negative result in the studies requested under a. and b.

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.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **24 November 2015**.

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 requirements. The scope of the present decision are the i*n vitro* gene mutation study in bacteria (Annex VII, 8.4.1. of the REACH Regulation), the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2 of the REACH Regulation) and the *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3. of the REACH Regulation). In accordance with Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, any registration for a substance manufactured or imported by a registrant at the tonnage level of 1000 tonnes or more per year shall contain this information.

1. Mutagenicity, *in vitro* gene mutation study in bacteria

The technical dossier contains an adaptation to the standard information requirement concerning *in vitro* gene mutation study in bacteria (Annex VII, 8.4.1.). The Registrant has sought to justify the adaptation with the following argument: "In accordance with section 1 of REACH (REGULATION (EC) No 1907/2006) Annex XI, the in vitro gene mutation study in bacteria (required in section 8.4.1) does not need to be conducted as there is sufficient weight of evidence from several independent sources of information leading to the conclusion that the substance is not mutagenic/genotoxic. Gluconate is an oxidative metabolite of glucose best known to occur in microorganisms, but also occurring in mammals (Rezzi et al., 2009). Glucose is oxidized to gluconate by glucose 1-dehydrogenase, which occurs in mammalian tissues (Harrison, 1931, 1932). Gluconate enters the pentose phosphate pathway via conversion to 6-phosphogluconate, a metabolic route of glucose catabolism. The formation of 6-phosphogluconate from exogenous gluconate has been demonstrated in mammals, demonstrating mammalian enzymatic capabilities for metabolizing gluconate (Stetten and Topper, 1953; Leder, 1957; Hakim and Moss, 1971; Casazza and Veech, 1986). Gluconokinase is the enzyme responsible for catalyzing the phosphorylation of gluconate to 6-phosphogluconate and has been identified in mammalian tissues, such as the brain and kidneys (Hakim and Moss, 1972). Thus, gluconate occurs endogenously from the oxidative metabolism of glucose and is utilized in a well-known biochemical pathway (the pentose phosphate pathway) of glucose catabolsim via the action of gluconokinase. Considering that gluconate is an endogenously occurring compound that is utilized by the body in a normal physiological process, studies addressing the mutagenicity/genotoxicity of gluconate are not deemed necessary as it is expected that the compound is not mutagenic/genotoxic." The Registrant provided a reference list to support his claims.

However, ECHA notes that references to information sources (which may or may not contain elements on which an adaptation could be justified) are not sufficient to demonstrate that the conditions of an adaptation are fulfilled. Thus, ECHA observes that there is no genotoxicity data provided in the technical dossier and no adequate and reliable documentation has been provided to support the presented argument. ECHA concludes that the adaptation argument does not fulfil the requirements of Annex XI and of introductory paragraph 4 of Annex VII of the REACH Regulation.

No valid adaptation was provided, and no test information for this endpoint is included in the registration dossier. Consequently there is an information gap and it is necessary to generate the data for this endpoint. Therefore, the Registrant is requested to submit the information for this endpoint using the above mentioned test method on the registered substance.

2. Mutagenicity, *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study

The technical dossier contains an adaptation to the standard information requirement concerning *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2.). The Registrant has sought to justify the adaptation in the same way as the adaptation for endpoint of Annex VII, 8.4.1. (see above under Section III.1.).

As explained under Section III.1., the information provided does not constitute a valid adaptation. Furthermore, no test information for this endpoint is included in the registration dossier. Consequently there is an information gap and it is necessary to generate the data for this endpoint. Therefore, the Registrant is requested to submit the information for this endpoint using one of the test methods mentioned under Section II.b. on the registered substance.

3. Mutagenicity, in vitro gene mutation study in mammalian cells.

According to Annex VIII, section 8.4.3. of the REACH Regulation, the *in vitro* gene mutation study in mammalian cells is required if there is a negative result in the *in vitro* studies specified under Annex VII, section 8.4.1 and Annex VIII, section 8.4.2.

The technical dossier contains an adaptation to the standard information requirement concerning *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.). The Registrant sought to justify the adaptation in the same way as the adaptations for the endpoints of Annex VII, 8.4.1. and Annex VIII, 8.4.2 (see above under Sections III.1. and 2).

As explained under Section III.1. the information provided does not constitute a valid adaptation. Furthermore no test information for this endpoint is included in the registration dossier. Consequently there is an information gap and it is necessary to generate the data for this endpoint. Therefore, the Registrant is requested to submit the information for this endpoint using the above mentioned test method on the registered substance provided there is a negative result in both studies requested under II.a. and II.b.

4. Comments and update submitted by the Registrant

Upon receipt of the draft decision pursuant to Article 50(1) the Registrant indicated his intent to improve his adaptation arguments in an updated registration dossier, which he intended to submit by 31 March 2013. The Registrant's latest update to the dossier was on 19 June 2013. In his update of the registration dossier the Registrant provided robust summaries named in the justification for data waiving and the reference list, respectively.

However, the provided study records give evidence about endogenous metabolism gluconate *in vitro* and *in vivo* without the indication of information leading to assumption/conclusion that a substance has or has not a mutagenic/genotoxic property. First, the record of study of Hakim and Moss (1974) confirmed *in vivo* metabolism of exogenous gluconate to 6-phosphogluconate in rat brain. Second, the record of study of Leder (1957) showed that gluconate was phosphorylated *in vitro* to 6-phosphogluconate in presence of ATP and Mg2+ by gluconokinase prepared from hog kidney. Third, the record of the study of Harrison (1932) confirmed gluconic acid was formed by *in vitro* oxidation of glucose in presence of activator [methylene blue] and glucose dehydrogenase extracted from liver. However, this publication stated also that "*glucose in presence of the dehydrogenase is not oxidised by molecular oxygen, but is oxidised in presence of methylene blue* and concluded that *gluconic acid may be a normal intermediary in the oxidation of glucose, an alternative possibility might be that the gluconic acid which has been isolated in these experiments may arise from some labile oxidation product of glucose which normally, in the intact cell, becomes further oxidised instead of appearing as gluconic acid*". Last, the record of the study of Rezzi (2009) presented an upward trend in gluconate, a key metabolite of pentose phosphate pathway (PPP) under caloric restriction (CR).

Thus, though there might be sufficient evidence provided by the Registrant that gluconate is an endogenously occurring compound that is utilised by the body in normal physiological process, the justification does not constitute a sufficient waiving argument for omission of the mutagenicity/genotoxicity studies with D-gluconic acid so that the studies could be deemed not necessary.

The Registrant also provided in his update of the registration dossier additional information: "*Finally, D-gluconic acid (E 574) / D-glucono-1,5 lactone (E 575) are permitted food additives under European Union law and can be used without restrictions according to the 'quantum satis' principle according to Commission Regulation 1129/2011 amending Annex II to Regulation 1333/2008 by establishing a Union list of food additives. Commission Regulation 231/2012 laying down specifications for food additives listed in Annexes II and III to Regulation 1333/2008 sets out the purity criteria to be respected. The substance(s) have in the past been assessed for their safety by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1999 http://www.inchem.org/documents/jecfa/jecmono/v042je12.htm and found as safe. The ADI (Acceptable Daily Intake) was set as 'not specified'.*"

ECHA observes that the assessment by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1999 and inclusion on the Annex II to Regulation 1333/2008 could possibly be considered as several independent sources of information. However, the data which might be included in those sources were not provided in the registration dossier. To conclude, the Registrant did not provide reliable, relevant and adequate data in his dossier to support data waiving justification. Therefore the Registrant has not fulfilled criteria of reliability, adequacy and relevance to justify weight of evidence adaptation for the mutagenicity/genotoxicity testing of D-gluconic acid. Thus, the testing may not be omitted on the basis of the information submitted.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by the Registrant and by other joint registrants 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 and that of joint Registrants to ensure that the joint registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In relation to the information required by the present decision, 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 who manufacture or import the same substance to agree on the appropriate composition of the test material 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 study must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the study 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 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://www.echa.europa.eu/web/guest/regulations/appeals. 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