Decision number: CCH-D-0000004423-80-05/F Helsinki, 25 August 2014

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

For trizinc dicitrate, CAS No 546-46-3 (EC No 208-901-2), 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 trizinc dicitrate, CAS No 546-46-3 (EC No 208-901-2), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100-1000 tonnes per year. This decision does not take into account any updates submitted after 6 March 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 registration at a later stage.

The compliance check was initiated on 10 July 2013.

On 22 November 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.

By 23 December 2013 the Registrant did not provide any comments on the draft decision to ECHA.
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, a proposal for amendment to the draft decision was submitted.

On 10 April 2014 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal for amendment received and did not amend section II of the draft decision but modified section III of the draft decision.

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

By 12 May 2014 the Registrant did not provide any comments on the proposals for amendment.

A unanimous agreement of the Member State Committee on the draft decision 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. Information required

A. Information in the technical dossier related to the identity of the substance

Pursuant to Articles 41(1), 41(3), 10(a)(ii) and Annex VI, Section 2 of the REACH Regulation the Registrant shall submit the following information for the registered substance subject to the present decision:

1. Composition of the substance (Annex VI, 2.3.);

2. Description of the analytical methods or the appropriate bibliographical references for the identification of the substance (Annex VI, 2.3.7.).

B. Information in the technical dossier derived from the application of Annexes VII to XI – requests for studies

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and/or (vii), 12(1)(d), 13 and Annexes VII, VIII, and 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. Relative density (Annex VII, 7.4.; test method: EU A.3./OECD 109);

2. *In vivo* eye irritation (Annex VIII, 8.2.1.; test method: OECD 405 as updated 2 October 2012);

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats;

4. *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. /OECD 471);

5. *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);

6. Screening study for reproductive/developmental toxicity (Annex VIII, 8.7.1.; test method: OECD 421 or 422) in rats, oral route; and

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

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.

C. Information in the technical dossier derived from the application of Annexes VII to XI – information related to robust study summaries

Pursuant to Articles 41(1), 41(3), and 10(a)(vii) of the REACH Regulation the Registrant shall submit robust study summaries for the following endpoints:

1. Acute toxicity by dermal route (Annex VIII, 8.5.3.);
2. *In vivo* skin irritation (Annex VIII, 8.1.1.); and
3. Skin sensitisation, *in vivo* testing (Annex VII, 8.3.(2)).

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 **1 September 2016.** The timeline has been set to allow for sequential testing as appropriate.

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.

A. Information in the technical dossier related to the identity of the substance

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

1. Composition of the substance

The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the corner stone of all the REACH obligations.

ECHA notes that the registration does not contain sufficient information for establishing the composition of the specific registered substance and therefore its identity, as required under Annex VI, Section 2.3. of the REACH Regulation. More specifically, the Registrant has indicated in the remarks field of the main constituent reported in Section 1.2 of the

technical dossier that the main constituent is "*Trizinc dicitrate typically as dihydrate or trihydrate*". The Registrant has not indicated that hydrates are within the scope of the substance registered by his legal entity based on the exemption for hydrates according to Annex V point 6 of the REACH Regulation. The Registrant shall note that when the specific provisions of Annex V point 6 for hydrates are being applied, information on the hydrated forms shall be reported in the registration dossier for the anhydrous substance. No compositional or quantitative analytical data was included in the dossier for the hydrated forms. This information is required if the Registrant intends to include hydrates within the scope of the registration for the anhydrous substance identified in section 1.1 of the dossier.

Consequently, the Registrant is requested to report each hydrate to be covered by the registration as a separate composition. Regarding how to report the composition of the registered substance in IUCLID, the following applies: The Registrant shall report the composition of the registered substance in IUCLID section 1.2. For each constituent required to be reported individually, the IUPAC name, CAS name and CAS number (if available), molecular and structural formula, as well as the minimum, maximum and typical concentration, shall be reported in the appropriate fields in IUCLID. Further technical details on how to report the composition in IUCLID are available in Data Submission Manual 18 on the ECHA website. The relevant sections being Q&A9 and paragraphs 2.1 and 2.2: http://echa.europa.eu/documents/10162/13653/substance_id_report_iuclid_en.pdf

Furthermore, ECHA notes that there is a discrepancy between the minimum purity of [redacted]% and the minimum concentration of the main constituent which is indicated to be [redacted]%. Consequently, the Registrant is required to clarify this discrepancy between the minimum purity and minimum concentration of the main constituent. The Registrant shall identify, quantify and report each constituent present at a concentration of 1% or greater in the composition.

2. Description of the analytical methods or the appropriate bibliographical references for the identification of the substance

"Description of the analytical methods or the appropriate bibliographical references for the identification of the substance" is a standard information requirement as laid down in Annex VI, Section 2.3.7. 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.

The registration did not contain sufficient details of the quantitative analysis for the substance which is required by Annex VI, Section 2.3.7. of the REACH Regulation. More specifically, while information on the quantification of the zinc cation is provided, results from the quantitative analysis of the citrate anion are absent and without this information, the composition of the substance reported in section 1.2 cannot be verified.

Furthermore, given the requirement of section A.1) of this decision to report each hydrate covered by the registration as a separate composition, quantitative chemical analysis (including quantification of crystalline water where appropriate) shall be provided for each composition listed in IUCLID section 1.2. The Registrant shall report the quantitative chemical analysis for each composition in IUCLID section 1.4.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit a description of the analytical methods or the appropriate bibliographical references for the identification of the substance subject to the present decision. The analytical data and details of the calculations used for quantification of the

citrate anion shall be provided. The composition and concentration ranges in IUCLID section 1.2 must be verifiable by the analytical information provided in IUCLID section 1.4.

B. Information in the technical dossier derived from the application of Annexes VII to XI – requests for studies

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII, VIII, and IX of the REACH Regulation.

1. Relative density (Annex VII, 7.4.; test method: EU A.3./OECD 109)

"Relative density" is a standard information requirement as laid down in Annex VII, Section 7.4. 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.

The Registrant used a read-across approach (Annex XI, Section 1.5.) in which the density value of the target substance was obtained by extrapolation from those of the source substances.

According to Annex XI, Section 1.5., first paragraph, the adaptation relying on a read-across approach "requires that physicochemical properties [...] may be predicted from data on reference substance(s) within the group by interpolation to other substances in the group." Extrapolation does not fall within this condition for a valid adaptation, so the read-across is not an adaptation that fulfils the information requirement.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Relative density (test method: EU A.3.) or density of liquids and solids (test method: EU A.3./OECD 109).

2. *In vivo* eye irritation (Annex VIII, 8.2.1.; test method: OECD 405 as updated 2 October 2012)

"*In vivo* eye irritation" is a standard information requirement as laid down in Annex VIII, Section 8.2.1. 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.

The Registrant has not provided any study record of an *in vivo* eye irritation study using the registered substance in the dossier that would meet the information requirement of Annex VIII, 8.2.1. Instead, the Registrant has sought to adapt this information requirement by applying read across (Annex XI, Section 1.5.) based on the results of the following studies:

- RCC, 1995: Study according to OECD Guideline 405 with the source substance trisodium citrate (CAS No 68-04-2, EC No 200-675-3); and

- Mirbeau et al., 1999 (EU RAR for zinc phosphate, 2008): Study according to EU Method B.5/ OECD Guideline 405 with the source substance trizinc bis(orthophosphate) (CAS No 7779-90-0, EC No 231-944-3).

ECHA notes that the Registrant did not provide any justification why the study showing the negative result for trizinc bis(orthophosphate) was selected for the read-across approach (Mirbeau et al., 1999); in particular, a justification is missing relating to why the EU Risk Assessment Reports (RARs) for zinc sulphate (severe ocular irritation), zinc oxide (borderline positive for irritation to the rabbit eye) and zinc distearate (not irritating) were not considered. Therefore, the justification and documentation provided for the read across are not considered to be adequate and reliable.

Furthermore, ECHA notes that the endpoint study record for Mirbeau et al., 1999 in the technical dossier does not meet the requirements of a robust stuy summary because it does not contain details in the following sections:

- Test materials: in paritcular, details on test material form;
- Test animals: in particular, details on environmental conditions;
- Test system: in particular, details on amount/ concentration applied, study design;
- Results and discussions: in partciular details on overall irritation/ corrosion results and irritant/ corrosive response data;
- Overall remarks, attachments; and
- Applicant's summary and conclusion.

Due to these deficiencies, ECHA cannot assess whether (a) the result of the proposed read across is adequate for the purpose of classification and labeling and/or risk assessment, (b) the result of the proposed read across does adequately and reliably cover the key parameters addressed in the test that is replaced and (c) the duration of exposure in the test with the source substance is comparable to or longer than the duration in the test with the target substance that is replaced.

For the reasons outlined above, ECHA concludes that the read across does not meet the requirements of Annex XI, Section 1.5. Therefore, the read across cannot be accepted.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Acute eye irritation/corrosion (test method: OECD 405 as updated 2 October 2012).

ECHA notes that further *in vitro* methods, including a range of OECD test guidelines and EU Test Methods, to address the eye irritation endpoint have been developed. Therefore, the Registrant should consider fulfilling the information requirement for *in vivo* eye irritation using the general rules for adaptation of Annex XI, Section 1.2. (Weight of Evidence) or Section 1.4 (*in vitro* methods) following the testing strategy as outlined in the supplement to the test method OECD 405 by using suitable regulatory approved *in vitro* methods. It is to be noted, that if the Registrant decides to follow this approach and obtains results that are suitable for classification and labelling and/or risk assessment, an adaptation for the *in vivo* test for eye irritation would need to be included in the updated technical dossier.

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats

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. Pursuant to last paragraph of Column 2 of that section, further studies may be required by the Agency in case of, for instance, indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation.

The Registrant has not provided any study record of a sub-chronic toxicity study (90-day) using the registered substance in the dossier that would meet the information requirement of Annex IX, Section 8.6.2. Instead, the Registrant has sought to adapt this information requirement by applying read across (Annex XI, Section 1.5.) based on the results of the following studies:

- [redacted], 1978 (IM 7855/B-0007855): Non-standard repeated dose toxicity study with the source substance citric acid (CAS No 77-92-9, EC No 201-069-1);
- [redacted], 1976 (IM 6743/B-0006743): Non-standard repeated dose toxicity study with the source substance citric acid (CAS No 77-92-9, EC No 201-069-1);
- [redacted], 1978 (IM 7855/B-0007855): Non-standard repeated dose toxicity study with the source substance citric acid (CAS No 77-92-9, EC No 201-069-1); and
- Maita et al., 1981 (EU RAR for zinc metal, 2008): Repeated dose toxicity study equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) with the source substance zinc sulphate (CAS No 7733-02-0, EC No 231-793-3).

The Registrant provided the following justification for the selection of zinc sulphate as the source substance: "*The physicochemical properties of zinc sulphate are considered to be more relevant to trizinc dicitrate than the monoglycerolate derivative.*" ECHA concludes that this statement is insufficient to justify the selection of zinc sulphate because it does not provide adequate and reliable documentation and justification to support the Registrant's claim. For this reason alone, the read across cannot be accepted.

In particular, it should be emphasised that the NOAEL for zinc monoglyceride is 13.26 mg Zn^{2+}/kg bw whereas that of zinc sulphate is 53.5 mg Zn^{2+}/kg bw according to the EU RAR for zinc metal (2008). ECHA notes that the selection of the NOAEL of zinc monoglyceride (13.26 mg Zn^{2+}/kg bw) would lead to an Risk Characterisation Ratio (RCR) > 1 for long-term - systemic effects, inhalation (cf. Chemical Safety Report, pages 44-46 and 98). This finding shows that the selection of the source substance is crucial for risk assessment to ensure safe use of the registered substance. Therefore, ECHA concludes that the read across cannot be accepted because adequate and reliable justification and documentation for the selection of the source substance is missing.

Furthermore, ECHA notes that the endpoint study record for Maita et al., 1981 in the technical dossier does not meet the requirements of a robust stuy summary because it does not contain details in the following sections:

- Test animals: in particular, details on test animals and environmental conditions;
- Administration/ exposure: in particular, details on vehicle, oral exposure, analytical verification of doses and concentrations, duration of treatment/ exposure, frequency of treatment, doses/ concentrations, number of animals per sex per dose, control animals, study design, and positive control;
- Examinations: in particular, details on observations and examinations performed and their frequency, sacrifice and pathology, other examinations, and statistical analysis;

- Resuls of examinations: in particular, details on clinical signs and mortality, body weight and weight gain, food consumption and compound intake, food efficiency, ophthalmoscopic examination, haematology, clinical chemistry, urinalysis, neurobehavior, organ weights, gross pathology, and histopathology (non-neoplastic and neoplastic);
- Overall remarks/ attachments; and
- Applicant's summary and conclusion.

Due to these deficiencies, ECHA cannot assess whether (a) the result of the proposed read across is adequate for the purpose of classification and labeling and/or risk assessment, (b) the result of the proposed read across does adequately and reliably cover the key parameters addressed in the test that is replaced, and (c) the duration of exposure in the test with the source substance is comparable to or longer than the duration in the test with the target substance that is replaced.

For the reasons outlined above, ECHA concludes that the read across does not meet the requirements of Annex XI, Section 1.5. Therefore, the read across cannot be accepted.

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

In light of the information provided on the uses and human exposure (no uses with spray application; uses resulting in oral exposure), ECHA considers that testing by the oral route is most appropriate.

According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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

4. *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. /OECD 471)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

The Registrant has not provided any study record of an *in vitro* gene mutation study in bacteria using the registered substance in the dossier that would meet the information requirement of Annex VII, 8.4.1. Instead, the Registrant has sought to adapt this information requirement by applying read across (Annex XI, Section 1.5.) based on the results of the following studies:

- Ishidate et al., 1984: Study equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) with the source substance sodium citrate (sodium dihydrogen citrate; CAS No 18996-35-5, EC No 242-734-6); and
- CCHRIS, 1992: Study equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) with the source substance citric acid, calcium salt (EC No 7693-13-2).

The two read-across studies included in the technical dossier address the presence of citrate anions only. The Registrant did not include any *in vitro* gene mutation study in bacteria in the technical dossier which was performed with a zinc(II) salt as test material. Furthermore, the technical dossier did not contain any reference to the EU RARs for *in vitro* genetic toxicity testing using zinc salts as test material.

With respect to the presence of zinc(II) cations, the Registrant states that *"information on the genetic toxicity of zinc is available in the RAR ASTDR Toxicity Profile (2005) and indicates that the zinc ions are not expected to contribute to genetic toxicity"* (cf. Section 7.6 of the technical dossier, Endpoint Summary: Genetic Toxicity). This statement is insufficient to meet the standard information requirement for this endpoint and cannot support the read across for zinc(II) cations because it does not provide any adequate and reliable documentation and justification.

Furthermore, ECHA notes that the Registrant used a general statement on genetic toxicity that "*zinc ions are not expected to contribute to genetic toxicity*". In this respect it should be emphasised that the read-across approach is endpoint specific and hence adequate and reliable justification and documentation should be provided that relate to the specific endpoint under consideration, i.e. *in vitro* gene mutation study in bacteria (Annex VII, 8.4.1.).

Due to the missing data on *in vitro* genetic toxicity studies in bacteria using zinc salts, ECHA cannot assess whether (a) the result of read-across is adequate for the purpose of classification and labelling and/or risk assessment, (b) the result of read-across does adequately and reliably cover the key parameters addressed in the test that is replaced; and (c) the duration of exposure in the tests with the source substances are comparable to or longer than the duration in the test with the target substance that is replaced.

The Registrant has not provided any study record of an *in vitro* gene mutation study in bacteria in the dossier that would meet the information requirement of Annex VII, Section 8.4.1. Instead, the Registrant has sought to adapt this information requirement by applying read across (Annex XI, Section 1.5.). However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, Section 1.5. as outlined above; in particular, the read across does not address the presence of zinc(II) cations. Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD 471).

5. *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)

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. 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.

The Registrant has not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study using the registered substance in the dossier that would meet the information requirement of Annex VIII, 8.4.2. Instead, the Registrant has sought to adapt this information requirement by applying read across (Annex XI, Section 1.5.) based on the results of the following studies:

- Yilmaz et al., 2008: Study equivalent or similar to OECD draft guideline 487 (2009) with the source substance citric acid (CAS No 77-92-9, EC No 201-069-1); and
- Ishidate et al., 1984: Study equivalent or similar to OECD Guideline 473 (*In vitro* Mammalian Chromosome Aberration Test) with the source substance citric acid (CAS No 77-92-9).

The two read-across studies included in the technical dossier address the presence of citrate anions only. The Registrant did not include any *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the technical dossier which was performed with a zinc(II) salt as test material. Furthermore, the technical dossier did not contain any reference to the EU RARs for *in vitro* genetic toxicity testing using zinc salts as test material.

ECHA notes that the technical dossier contained also an *in vivo* study equivalent or similar to OECD Guideline 475 (Mammalian Bone Marrow Chromosome Aberration Test; Litton Bionetics, 1975) and an *in vivo* study equivalent or similar to EU Method B.22 (Rodent Dominant Lethal Test; Litton Bionetics, 1975). However, also these *in vivo* studies were performed with the source substance citric acid only. No *in vivo* study for genetic toxicity using a zinc(II) salt was provided in the technical dossier.

With respect to the presence of zinc(II) cations, the Registrant merely states that *"information on the genetic toxicity of zinc is available in the RAR ASTDR Toxicity Profile (2005) and indicates that the zinc ions are not expected to contribute to genetic toxicity"* (cf. Section 7.6 of the technical dossier, Endpoint Summary: Genetic Toxicity). ECHA notes that this statement is insufficient to meet the standard information requirement for this endpoint and to justify the read across for zinc(II) cations because it does not provide any adequate and reliable documentation and justification. Therefore, the read across cannot be accepted.

Furthermore, the Registrant used a general statement on genetic toxicity that *"zinc ions are not expected to contribute to genetic toxicity"*. In this respect, ECHA emphasises that the read-across approach is endpoint specific and hence adequate and reliable justification and documentation should be provided that relate to the specific endpoint under consideration, i.e. *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2.).

Due to the missing data on *in vitro* cytogenicity studies in mammalian cells or *in vitro* micronucleus studies using zinc salts (or adequate *in vivo* studies using zinc salts), ECHA cannot assess whether (a) the result of read-across is adequate for the purpose of classification and labelling and/or risk assessment, (b) the result of read-across does adequately and reliably cover the key parameters addressed in the test that is replaced, and (c) the duration of exposure in the tests with the source substances are comparable to or longer than the duration in the test with the target substance that is replaced.

The Registrant has not provided any study record for an *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study in the dossier that would meet the

information requirement of Annex VIII, Section 8.4.2. Instead, the Registrant has sought to adapt this information requirement by applying read across (Annex XI, Section 1.5.). However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, Section 1.5. as outlined above; in particular, the read across does not address the presence of zinc(II) cations. Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* cytogenicity study in mammalian cells (test method: EU B.10./OECD 473) or *in vitro* mammalian cell micronucleus study (test method: OECD 487).

6. Screening study for reproductive/developmental toxicity (Annex VIII, 8.7.1.; test method: OECD 421 or 422) in rats, oral route

"Screening for reproductive/developmental toxicity" is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant.

The Registrant has not provided any study record for a screening study for reproductive/ developmental toxicity using the registered substance in the dossier that would meet the information requirement of Annex VIII, 8.7.1. Instead, the Registrant has sought to adapt this information requirement by applying weight-of-evidence/read across (Annex XI, Section 1.2. and 1.5.) as well as adpatation according to Annex XI, 1.1.2. based on the results of the following studies:

- Wright and Hughes, 1976: Non-standard repeat dose feeding study with the source substance citric acid (CAS No 77-92-9, EC No 201-069-1);
- Bonting, 1956: Non-standard repeat dose feeding study with the source substance citric acid (CAS No 77-92-9, EC No 201-069-1); and
- Maita et al., 1981 (EU RAR for zinc metal, 2008): Repeated dose toxicity study equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) with the source substance zinc sulphate (CAS No 7733-02-0, EC No 231-793-3).

Furthermore, The Registrant provided the following waiving statement: *"In accordance with Section 1.1.2 of REACH Annex XI, the 2-generation reproductive toxicity study (required in Section 8.7.3) does not need to be conducted because existing data are adequate for the purposes of classification and labelling and risk assessment. The effect of trizinc dicitrate is not expected to differ significantly from the effects of the zinc ions and citric acid separately once absorbed. Since the known toxicological effects of citric acid are negligible, the toxicological effects of trizinc dicitrate are therefore derived from the zinc cation. Based on the reported toxicological test data for zinc, it can be concluded that it is unlikely that trizinc dicitrate would impair fertility."*

According to the Registrant, zinc sulphate heptahydrate in dietary concentrations up to 30,000 mg/kg feed did not produce adverse effects on either male or female sex organs after 13 weeks of exposure (Maita et al., 1981). However, the Registrant did not provide a robust study summary for Maita et al, 1981 (see issue on repeated dose toxicity above).

With respect to the studies using the source substance citric acid (Wright and Hughes, 1976; Bonting, 1956), it is not clear from the provided study summaries what kind of studies were conducted due to poor reporting. For example it seems doubtful that the studies are indeed two-generation reproductive toxicity studies as stated in the technical dossier. Furthermore, in both studies only very limited parameters were measured (number of young born and their subsequent survival up to the weaning). Due to the poor reporting on the studies using citric acid as source substance (Wright and Hughes, 1976; Bonting, 1956) and the missing robust study summary for Maita et al., 1981, ECHA cannot assess whether (a) the result of the proposed read across is adequate for the purpose of classification and labelling and/or risk assessment, (b) the result of the proposed read across does adequately and reliably cover the key parameters addressed in the test that is replaced (c) and the duration of exposure in the test with the source substance is comparable to or longer than the duration in the test with the target substance that is replaced.

Therefore, ECHA concludes that the weight of evidence/ read across (Annexes XI, Sections 1.2. and 1.5.) and adaptation according to Annex XI, 1.1.2. cannot be accepted.

In particular, it cannot be assessed whether Maita et al., 1981 can be used to conclude on the outcome that "no adverse effects on reproductive organs or tissues" were observed. However, ECHA emphasises that the screening study for reproductive/developmental toxicity according to Annex VIII, Section 8.7.1. cannot be adapted on the basis of absence of adverse effects on reproductive organs and tissues in repeated dose toxicity studies only (cf. Annex IX, Section 8.7.3., Column 1).

Furthermore, ECHA notes that according to the EU RARs for zinc salts *"no 1- or 2-generation studies are available*" for zinc. And the ATSDR, 2005 ("Toxicological profile for zinc", page 109) states that "*increased pre-implantation loss and reproductive dysfunction in rats were observed in oral exposure studies* (Pal and Pal 1987; Sutton and Nelson 1937)" and "*an oral reproductive toxicity study in a [...] a multigeneration study, including reproductive organ pathology, would be useful for determining whether oral zinc exposure is likely to cause reproductive toxicity in humans.*" These reports indicate that there is a lack of data with respect to reproductive toxicity for zinc salts in general.

ECHA concludes that for the reasons outlined above, the weight of evidence and read across arguments presented by the Registrant cannot be accepted.

The Registrant has not provided any study record of a screening study for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1. Instead, the Registrant has sought to adapt this information requirement by applying weight of evidence and read across (Annex XI, Sections 1.2. and 1.5.) and refering to Annex XI, Sextion 1.1.2. However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, Sections 1.1.2., 1.2. and 1.5. as outlined above; in particular, the adaptation lacks adequate and reliable documentation and justification. Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

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

According to the test methods OECD 421/422, the test guideline is designed for use with the rat and the substance is administered orally unless other routes of administration are

considered more appropriate. ECHA considers these default parameters appropriate and testing should be performed on the rat by the oral route.

ECHA notes that the following reproductive toxicity endpoints are not addressed by the pre-natal developmental toxicity study (requested in Section II.7): mating behaviour, fertility and peri-natal effects whereas they are addressed by the screening study for reproductive/developmental toxicity (OECD 421 or 422).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit information derived with the registered substance subject to the present decision: **Either** the reproductive/developmental toxicity screening test (test method: OECD 421) in rats by the oral route, **or** the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD 422) in rats by the oral route.

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

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

The Registrant has not provided any study record of a pre-natal developmental toxicity study using the registered substance in the dossier that would meet the information requirement of Annex IX, 8.7.2. Instead, the Registrant has sought to adapt this information requirement by applying weight-of-evidence/read across (Annex XI, Section 1.2. and 1.5.) as well as adpatation according to Annex XI, 1.1.2. based on the results of the following studies:

- Food & Drug Research Laboratories, Inc., 1973, Contract No 71-260: Study equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study) with the source substance citric acid (CAS No 77-92-9, EC No 201-069-1) in mice, rats, rabbits and hamsters;
- Food & Drug Research Laboratories, Inc., 1973, Report No PB-267 191 (EU RAR zinc metal, 2008): Non-standard study with the source substance zinc sulphate (CAS No 7733-02-0, EC No 231-793-3); and
- Food & Drug Research Laboratories, Inc., 1974, Report No PD-221805 (EU RAR zinc metal, 2008): Non-standard study with the source substance zinc sulphate (CAS No 7733-02-0, EC No 231-793-3).

Furthermore, the Registrant provided the following waiving statement: *"In accordance with Section 1.1.2 of REACH Annex XI, the pre-natal developmental toxicity study (required in Section 8.7.2) does not need to be conducted because existing data are adequate for the purposes of classification and labelling and risk assessment. The effect of trizinc dicitrate is not expected to differ significantly from the effects of the zinc ions and citric acid separately once absorbed. Since the known toxicological effects of citric acid are negligible, the toxicological effects of trizinc dicitrate are therefore derived from the zinc cation. Based on the reported toxicological test data for zinc , it can be concluded that it is unlikely that trizinc dicitrate would cause developmental effects."*

ECHA notes that the endpoint study records for the studies conducted with zinc sulphate (Food & Drug Research Laboratories, Inc., 1973, Report No PB-267 191 and Food & Drug Research Laboratories, Inc., 1974, Report No PD-221805) in the technical dossier do not

meet the requirements of a robust stuy summary (e.g. the Registrant has not provided adequate information on the following: test material form, details on test animals and environmental conditions, vehicle, details on exposure, details on analytical verification of doses or concentrations, details on mating procedure, control animals, maternal examinations, ovaries and uterine content, fetal examinations, statistics, indices, and historical control data). Due to the missing robust study summaries, ECHA cannot assess whether (a) the result of the proposed read across is adequate for the purpose of classification and labeling and/or risk assessment, (b) the result of the proposed read across does adequately and reliably cover the key parameters addressed in the test that is replaced, and (c) the duration of exposure in the test with the source substance is comparable to or longer than the duration in the test with the target substance that is replaced.

Therefore, ECHA concludes that the weight of evidence/ read across (Annexes XI, Sections 1.2. and 1.5.) and adaptation according to Annex XI, Section 1.1.2. can not be accepted.

ECHA emphasises that ATSDR, 2005 ("toxicological profile for zinc", pages 109-110) discloses that (a) "*in a very brief report of a human study in which pregnant women received high-doses of zinc supplements during the last trimester of pregnancy, an increased incidence of stillbirths and one premature delivery were observed* (Kumar 1976)", (b) "*increased fetal resorptions were observed in rats after oral exposure to zinc* (Schlicker and Cox 1968)", and (c) "*additional inhalation, oral, and dermal exposure studies in animals would be useful to predict whether developmental effects should be a concern for humans exposed to zinc.*" This report indicates that there is a lack of data with respect to developmental toxicity for zinc salts in general.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2. Instead, the Registrant has sought to adapt this information requirement by applying weight of evidence and read across (Annex XI, Sections 1.2. and 1.5.) and Annex XI, Section 1.1.2. However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, Sections 1.1.2., 1.2. and 1.5. as outlined above; in particular, the adaptation lacks adquate and reliable documentation and justification. Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. 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 (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in rats or rabbits by the oral route.

8. Timeline set for sequential testing

As stated in Section II, the timeline has been set to allow for sequential testing: The Registrant should consider conducting the studies requested under Section II sequentially in an order that allows the Registrant to consider all adaptation possibilities that may arise during the sequential testing, in particular the fourth indent of Column 2 of Section 8.7.1 of Annex VIII. The Registrant may wish to refer to the available guidance material, in particular ECHA's Guidance on information requirements and chemical safety assessment, Chapter R.7a, Section 7.6.6.3.

C. Information in the technical dossier derived from the application of Annexes VII to XI – information related to robust study summaries

According to Article 3(28) of the REACH Regulation, a robust study summary means "a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report". For the endpoints listed below, the data on test conditions, protocol deviations and/or conclusions were not sufficient to make an independent assessment of the study and thus did not meet the requirements of a robust study summary within the meaning of Article 3(28). The Registrant is requested to provide the data according to Article 3(28) as outlined below.

1. Acute toxicity by dermal route (Annex VIII, 8.5.3.

The robust study summary for the weight-of-evidence/ read-across study "Zinc distearate RAR (2008). Risk Assessment Report zinc distearate (CAS 557-05-1)" does not contain details in the sections 'Materials and methods', 'Test materials', 'Test animals', 'Administration/ exposure', 'Results and discussions', 'Overall remarks, attachments', and 'Applicant's summary and conclusion'. For instance, the principles of the method (non-guideline study) should be specified and details on test material and its form, test animals and environmental conditions, type of coverage and vehicle used for adminsitration, duration of exposure, doses, number of animals per sex per dose, control animals, study design, statistical analysis, basis for LD_{50} derivation, mortalilty, clinical signs, body weight, and gross pathology should be provided. Appropriate summaries explaining the main findings should be given.

2. *In vivo* skin irritation (Annex VIII, 8.1.1.)

The robust study summary for the weight-of-evidence/ read-across studies "van Huygevoort, 1999; Lansdown ABG, 1991; Zinc sulphate RAR (2008)" does not contain details in the sections 'Materials and methods', 'Test materials', 'Test animals', 'Administration/ exposure', 'Results and discussions', 'Overall remarks, attachments', and 'Applicant's summary and conclusion'. For instance, details on test material and its form, species and strain of test animals, environmental conditions, type of coverage, preparation of test site, vehicle, amount/ concentration applied, duration of treatment/ exposure, observation period, number of animals, control animals, study design, irritant/ corrosive responses, and other effects if observed should be provided. Appropriate summaries explaining the main findings should be given.

3. Skin sensitisation, *in vivo* testing (Annex VII, 8.3.(2))

The robust study summary for the weight-of-evidence/ read-across studies " van Huygevoort AHBM, 1999; Zinc sulphate RAR (2008)" does not contain details in the sections

'Materials and methods', 'Test materials', 'Test animals', 'Administration/ exposure', 'Results and discussions', 'Overall remarks, attachments', and 'Applicant's summary and conclusion'.

For instance, details on test material and its form, test animals and environmental conditions, details on study design, challenge controls, positive control substance(s), positive control results, and results of test (table) should be provided. Appropriate summaries explaining the main findings should be given.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted 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.

In relation to the information required by the present decision, 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 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 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. 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.

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