Decision number: CCH-D-0000003520-85-05/F Helsinki, 25 February 2014

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

**For 1,3,5-triazine-2,4,6(1H,3H,5H)-trione, compound with 1,3,5-triazine-2,4,6-triamine (1:1), CAS No 37640-57-6 (EC No 253-575-7), 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 1,3,5-triazine-2,4,6(1H,3H,5H)-trione, compound with 1,3,5-triazine-2,4,6-triamine (1:1), CAS No 37640-57-6 (EC No 253-575-7), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the following standard information requirements relating to "Aquatic toxicity" and related environmental hazard assessment (Annex IX, 9.1.5. and 9.1.6., and Annex I, Section 3.3. of the REACH Regulation).

This decision is based on the registration dossier as submitted with latest submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates after 5 September 2013, 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 28 February 2013.

On 11 June 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.

On 9 July 2013 ECHA received comments from the Registrant agreeing to ECHA's draft decision but requesting prolongation for the deadline given in Section II.

ECHA considered the Registrant's comments received. On basis of this information, the deadline in Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 5 September 2013 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 to amend the draft decision within 30 days of the receipt of the notification.

By 7 October 2013, a Competent Authority of the Member State submitted a proposal for amendment to the draft decision.

On 11 October 2013 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal for amendment received and amended the draft decision.

On 21 October 2013 ECHA referred the draft decision to the Member State Committee

By 11 November the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 25 November 2013 in a written procedure launched on 14 November 2013. 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)(d), 13 as well as Annex IX of the REACH Regulation the Registrant is required to carry out the following studies using the indicated test methods and the registered substance subject to the present decision:

a. Long-term toxicity testing on fish (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210); and
b. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

Pursuant to Articles 41(1)(c), 41(3), 10(b) and 14 as well as Annex I, 3.3. of the REACH Regulation the Registrant shall submit the following information:

c. PNECs for the aquatic compartment on the basis of data from a. and b. above as it becomes available.

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 **25 August 2016.**

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 scope of the present decision covers Annex IX, 9.1.5. and 9.1.6. as well as related environmental hazard assessment. In accordance with Articles 10(a)(vii), (b), 12(1) and 14(1) of the REACH Regulation, the registration is required to contain this information.

*a. and b. Long-term aquatic toxicity testing on invertebrates and fish*

According to column 1 of Sections 9.1.5. and 9.1.6. of Annex IX of the REACH Regulation, long-term toxicity testing on invertebrates and on fish is required to fulfil the standard information requirements.

The Registrant sought to fulfil these information requirements on aquatic long-term toxicity of the substance from the application of studies using for Fish:

- Acute and subacute toxicity to rainbow trout;
- The application of egg-larval development of the fresh water fish *Jordanella floridae*, and for aquatic Invertebrates;
- The acute and chronic toxicity of melamine (2,4,6-triamino-triazine) to *Daphnia magna* using Dutch proposed standards NEN 6501 and 6502.

ECHA notes that the aquatic toxicity studies were carried out on a proposed analogue substance.

Aquatic toxicity studies on Fish can be only regarded as long-term when the sensitive life-stages (juveniles, eggs, larvae) are exposed. For aquatic toxicity studies on Invertebrates at least two broods (depending on the species even more) need to be exposed so that the study can be considered as long-term. (ECHA Guidance on information requirements and chemical safety assessment, pages 25, 26 of Chapter R. 7B (version 1.2., November 2012)).

The submitted information does not suffice to fulfil the two endpoints in question:

- Annex IX, Section 9.1.6. – fish: Firstly, none of the submitted fish studies covers all sensitive life-stages. Secondly, even looking at all submitted fish studies together, all different sensitive life-stages are not covered so that no weight-of-evidence argument could be applied.
- Annex IX, Section 9.1.5. – aquatic invertebrates: The acute and chronic toxicity studies do not cover two broods and can therefore not be recognised as long-term study. The Registrant also has not submitted a weight-of-evidence argument.

As the information provided would not even fulfil the information requirement for the analogue substance, ECHA stresses that at this stage it has not assessed the Registrant's justification for proposing a read-across from the analogue substance.

As the submitted information does not fulfil the information requirements, there are information gaps and it is necessary to provide information for the endpoints in order to bring the registration dossier into compliance with relevant information requirements.

A Member State Competent Authority proposed to amend the decision and remove all references to the integrated testing strategy because there are indications that if both compounds 1,3,5-triazine-2,4,6(1H,3H,5H)-trione and 1,3,5-triazine-2,4,6-triamine are administered together they form poorly soluble renal crystals (e.g. in fish and humans) which can cause renal failure. As *Daphnia* does not have kidneys they are not suitable to assess this effect. Therefore, both tests on fish and *Daphnia* should be conducted. Three publications were indicated in the the proposal for amendment received (R. Reimschuessel *et al.*, 2010; "Renal crystal formation after combined or sequential oral administration of melamine and cyanuric acid "; Brown, C. A., K. S. Jeong, *et al.* (2007). "Outbreaks of renal failure associated with melamine and cyanuric acid in dogs and cats in 2004 and 2007";

R. Reimschuessel *et al.* 2008; "Evaluation of the renal effects of experimental feeding of melamine and cyanuric acid to fish and pigs Center for Veterinary Medicine, US FDA, USA.; American Journal of Veterinary Research, 10/2008; 69(9):1217-28."). The latter publication was quoted as "Although melamine and cyanuric acid appeared to have low toxicity when administered separately, they induced extensive renal crystal formation when administered together. The subsequent renal failure may be similar to acute uric acid nephropathy in humans, in which crystal spherulites obstruct renal tubules".

The Registrant, in his comments to the proposal for amendment, disagreed with the Member State Competent Authority and made reference to four publications; Stine, C. B. *et al.* (2013). "Depletion of melamine and cyanuric acid in kidney of catfish Ictalurus punctatus and trout Oncorhynchus mykiss"; Reimschuessel, R. *et al.* (2008). "Residue depletion of melamine and cyanuris acid in catfish and rainbow trout following oral administration". Reimschuessel, R. *et al.* (2010). "Renal crystal formation after combined or sequential oral administration of melamine and cyanuric acid"; Stine, C. B. *et al.* (2012). "Depletion of melamine and cyanuric acid in serum from catfish Ictalurus punctatus and rainbow trout Oncorhynchus mykiss".

The Registrant in his comments to the proposal for amendment, agrees that the published GLP studies in channel catfish (*Ictalurus punctatus*) and rainbow trout (*Oncorhynchus mykiss*) conducted by the US FDA by single gavage doses of 20 mg/kg body weight of melamine, cyanuric acid, or 20 mg/kg body weight of both compounds simultaneously clearly show that the combined doses of melamine and cyanuric acid lead to the formation of renal melamine cyanurate crystals.

The Registrant states in his comments to the proposal for amendment, "Even trout with the highest levels of crystals did not show adverse health effects although they most likely were in renal failure. It is known, that renal failure can be fatal in mammals but fish can excrete nitrogenous wastes across their gill membranes which might be the reason for the absence of any adverse health effects". Whilst ECHA agrees with the general statement from the Registrant that fish can excrete nitrogenous wastes via the gills, the Registrant does not provide specific quantitative information verifying that this is the case for the registered substance considering the molecualr weight of the registered substance.

The Registrant further states in his comments to the proposal for amendment "It can be expected that the US FDA studies that used a single gavage dose of 20 mg/kg body weight of both compounds simultaneously represent a worst case condition and exposure via dissolved test substance in water will not result in comparable internal concentrations of the compound. Therefore, it is not believed that a long-term toxicity test according to OECD guideline 210 would reveal any adverse health effect on fish due to the fact that the internal concentrations in fish during the OECD 210 study will not reach the gavage dose of the FDA study and even this dose did not result in adverse health effects". Although a 20 mg/kg dose can be considered as high, ECHA disagrees that a single exposure can represent a worst case scenario. Compared to such single exposure, the Registrant has not provided argumentation that continuous water-born exposure could not result in a more severe exposure, resulting in a higher impact on the exposed fish population. Due to the publications stated by both the Registrant and the Member State Competent Authority, ECHA understands that indeed fish may be considered as a group of organisms with a potential higher sensitivity to the registered substance indicating the need to investigate further chronic effects.

In light of this, ECHA agrees with the Member State Competent Authority reasoning and considers that the integrated testing strategy addressed in the ECHA Guidance on information requirements and chemical safety assessment (version 1.2., November 2012), Chapter R7b (Section R.7.8.5., pages 32-57, including Figure R.7.8-4 on page 56), is not applicable to the specific case at hand. An assessment of the renal crystal formation, a specific effect to the registered substance, cannot be established in *Daphnia*, as they do not have kidneys and therefore cannot be considered to fulfill any of the adaptation possibilities listed in Annex IX, 9.1., Column 2 or the specific rules for adaptation of Annex XI, Section 1.

Both studies, Long-term toxicity testing on fish (Annex IX, 9.1.6.1.) Fish, early-life stage toxicity test, OECD 210) and Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.) *Daphnia magna* reproduction test, EU C.20/OECD 211) are standard information requirements and the Registrant did not include acceptable adaptations in his Registration dossier on chronic toxicity.

Therefore, pursuant to Article 41(3) of the REACH Regulation, the Registrant is requested to submit information using the following test methods on the registered substance:

- Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211); and
  Long-term toxicity testing on fish (Annex IX, 9.1.6.1; test method: Fish, early-life stage toxicity test, OECD 210).

*c. PNECs for the aquatic compartment*

Annex I, Section 3.3. of the REACH Regulation requires the Registrant to establish predicted no effect concentrations (PNEC(s)) for the registered substance, covering each environmental sphere, including the aquatic compartment.

ECHA notes that the registration submitted by the Registrant contains no PNEC for the aquatic compartment. Instead of providing a PNEC the registrant sought to justify why not providing a PNEC, stating in the PNEC field: 'No data: aquatic toxicity unlikely' and included a further justification for not deriving PNECs. However, pursuant to Annex I, Section 3.3.2., the only possibility to exempt from deriving PNEC(s) is to fully justify why it is not possible to do so. The Registrant has not claimed that the derivation of PNEC(s) is not possible and is therefore required to derive PNECs (Annex I, Section 3.3.1.).

The Registrant shall therefore provide aquatic PNEC derivations in line with the provisions of Annex I. They shall be kept updated, along with the whole Chemical Safety Report. In particular, when data becomes available from the studies required under Section II.a. and b. it shall be taken into consideration in an updated derivation of the PNECs.

When deriving the PNECs, the Registrant shall choose an appropriate Assessment Factor taking into account footnote to Annex I, Section 3.3.1 and also ECHA Guidance chapter R.10, Section R.10.3.1.2.

**Deadline for submitting the required information**

In the draft decision, ECHA indicated that the Registrant should submit the required information to ECHA in an updated registration dossier within 18 months from the date of the final decision. In its comments, the Registrant requested to prolong the timeline from 18 to 36 months. The Registrant based its request on issues related to the laboratory capacity and on the time frame for the development of the analytical method.

ECHA accepts the Registrant's argument that a 9 months scheduling phase is necessary. However, the argument that further 9 months are needed to develop an anlytical method and pre-test was considered excessive. ECHA considers that 6 months in addition to the 9 months provided for scheduling purposes are sufficient.

Furthermore, ECHA agrees to the fact that consecutive testing should be possible. On this basis, ECHA agrees to the 6 months period that the Registrant suggests for conducting the Daphnia test. However, ECHA does not agree with the Registrant's additional suggestion to allow 12 further months for performing the Fish test as the analyticial set up should be already finalised and the experimental set-up from the Daphnia test can also be applied. ECHA considers 9 months adequate for performing consecutively the Fish test.

Therefore, ECHA acknowledges the Registrant's request to extend the deadline due to substance properties and issues with test laboratory facilities and agrees to extend the timeline from 18 months to 30 months.

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.

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. General requirements for the generation of information

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://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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