EUROPEAN CHEMICALS AGENCY

Helsinki, 30 March 2017

Addressee: [redacted]

Decision number: CCH-D-2114355438-42-01/F
Substance name: 2,4,6-trichloro-1,3,5-triazine
EC number: 203-614-9
CAS number: 108-77-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 20.08.2015
Registered tonnage band: 1000 tonnes or more per year

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3. test method: EU B.56./OECD TG 443) in rats, oral route; with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbits), oral route with the registered substance;**

3. **Classification and labelling (Annex VI, Section 4.):**
   - apply classification and labelling on the registered substance for repeated dose toxicity or provide a justification for not classifying;

You 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 and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **7 October 2019**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.]

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, your technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

You have sought to adapt this information requirement by referring to Annex XI, Section 1. While you have not explicitly claimed a specific adaptation under Section 1 of Annex XI, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2. You provided the following justification for the adaptation:

"In accordance with column 1 of REACH Annex X, 8.7.3, an extended one generation or two generation reproduction toxicity study is required. According to Regulation (EC) No.1907/2006, Annex XI, 1., standard data requirements can be adapted in case testing does not appear scientifically necessary. For Cyanuric chloride no adverse effects on reproduction and development organs were observed in available repeated dose toxicity and developmental toxicity studies.

In a repeated oral toxicity study (no guideline followed) rats were treated on 5 consecutive days with Cyanuric chloride (93-0090-FKR). No systemic toxicity was found. Effects were only seen at the portal of entry based on the irritation and caustic effects of Cyanuric chloride. In a subchronic inhalation toxicity study (OECD 413) no clear treatment related effect became obvious (94-0211-DKT). In a dermal toxicity study (OECD 410) rabbits were treated repeatedly during 21 days (83-0093-FKT). Generally, effects were only seen at the portal of entry based on the irritation and caustic effects of Cyanuric chloride.

The teratogenicity/pre-natal developmental toxicity study according to OECD 414 (83-0091-FGT) indicated adverse effects on embryo/fetal development only in combination with severe maternal toxicity.

In conclusion, the available studies do not show any adverse signs on reproductive organs or embryonic/fetal development at non-maternal toxicity, so further testing (e.g. extended one generation or two generation reproduction study) is not expected to provide any useful new knowledge for this substance and thus not justified, also considering animal welfare reasons."

Adaptation based on Annex XI, Section 1.2. requires that based on information from several independent sources it can be assumed/concluded that the substance has or has not a particular dangerous property, in this case for reproductive toxicity. In your justification you refer to data provided for other endpoints in your registration dossier (repeated dose toxicity studies, dermal toxicity study, and a pre-natal developmental toxicity study). ECHA has assessed the weight of each of these lines of evidence separately and together, and the conclusions of this assessment are reported below.

Regarding effects on functional fertility (i.e. sexual function and fertility) after an exposure during full spermatogeneisis and folliculogenesis (e.g. mating index, fertility index, gestation index, gestation length, litter size, abortions), the information provided is very limited consisting only of effects on maintenance of pregnancy and intrauterine development of the foetuses stemming from the prenatal developmental toxicity study and, thus, for limited aspects on reproductive toxicity only and addressing limited life stages due to gestational exposure phase. In addition, you did not provide any information on potential hazardous effects on postnatal development including sexual maturation and histopathological integrity of the reproductive organs at adulthood. The repeated dose toxicity studies and the dermal studies do not provide any information with regard to functional fertility. The repeated dose toxicity studies may provide histopathological investigations of reproductive organs in adult animals but not any information on effects in their offspring after *in utero* and postnatal exposure. Furthermore, information on oestrous cycle and sperm parameters and information on endocrine modes of action is missing.

According to your assessment, the prenatal developmental toxicity study indicated "*adverse effects on embryo/fetal development only in combination with severe maternal toxicity*". The maternal toxicity effects in the pre-natal developmental toxicity study were: "*in the high dose group: dry brown, red or black matter around eyes, nose, mouth, face, forelimbs or anogenital area; exess salivation; matted haircoat; respiratory rales*" and "*body weight: slightly reduced body weight gain in the high dose group*". Thus, adverse effects on embryo/foetal development was observed at the same dose level than maternal toxicity, but based on information provided it cannot be excluded that the findings reflects reproductive toxicity of the registered substance.

Taking into account the above very limited information provided on reproductive toxicity, ECHA considers that your conclusion that "*the available studies do not show any adverse signs on reproductive organs or embryonic/fetal development at non-maternal toxicity, so further testing (e.g. extended one generation or two generation reproduction study) is not expected to provide any useful new knowledge for this substance and thus not justified, also considering animal welfare reasons*" is not adequately supported by the data, and it cannot be assumed/concluded that the substance is not a reproductive toxicant. Furthermore, there is a particular concern for developmental immunotoxicity and information for this endpoint is not provided.

Upon the submission of the draft decision you submitted comments and proposed to use read-across to adapt the standard information requirements (REACH Annex X, section 8.7.3 and Annex X, section 8.7.2), in accordance with the provisions of Annex XI, 1.5 of the REACH Regulation.

According to Annex XI, Section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). The similarities may be on the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals. Furthermore, Annex XI, Section 1.5. lists several additional requirements, including that adequate and reliable documentation of the applied method have to be provided.

You based your hypothesis on the transformation to common compounds, i.e. the target substance cyanuric chloride undergoes a rapid and stepwise hydrolysis to cyanuric acid. Therefore, you considered that the studies with the source compound cyanuric acid can be used to predict the effects that would be observed in a study with the target substance cyanuric chloride.
To support your hypothesis you provided:
-hydrolysis data showing the stepwise hydrolysis leading to the intermediate products identified as 2,4-dichloro-6-hydroxy-1,3,5-triazine, 2-chloro-4,6- dihydroxy-1,3,5-triazine and finally to cyanuric acid.
- an OECD Toolbox profiling for target and source substance as well as for the intermediate degradation products
-a comparison of the structures and physicochemical properties of the target and source substance.
-a comparison of the target and source substance toxicities for the endpoints acute (oral and inhalation), skin and eye irritation and sensitisation.

With regard to the hydrolysis data, ECHA notes that while the first hydrolysis step is indeed fast (DT50 = 0.7 minutes at pH 2.0, and 30°C, and DT50 = 1.2 minutes at pH 7.0, and 35°C) the exposure to the intermediate compounds from the following two hydrolysis steps cannot be neglected as a DT50 of 30 and 75 minutes respectively was determined at pH 2.0 and 30°C. You further explained that "*Increasing the temperature and lowering the pH results in a faster step-wise hydrolysis of cyanuric chloride into its degradation products.*" You claimed that "*Since the hydrolysis of cyanuric chloride, especially the first hydrolysis step, is very fast, the intermediate degradation products of cyanuric chloride are considered to be less relevant for potential systemic effects under physiological conditions.*" and that "*Due to the rapid degradation of cyanuric chloride to cyanuric acid under acidic conditions, oral exposure to cyanuric acid likely results in systemic exposure to the final degradation product cyanuric acid under physiological conditions.*"

However, there are no hydrolysis rate data for the last two hydrolysis steps in low pH and at body-like temperature to clarify the extent of exposure to the intermediate products. Therefore, your conclusions are purely theoretical and it cannot be concluded that the rate is fast enough to exclude (systemic) exposure to the intermediate hydrolysis products.

You provided an OECD Toolbox profiling for target and source substance as well as for the intermediate degradation products 2,4-dichloro-6-hydroxy-1,3,5-triazine and 2-chloro-4,6-dihydroxy-1,3,5-triazine showing similarity in the selected parameters.

You also explained that the source and target compounds are structurally related, with the only structural difference in the absence of chlorine in the source substance which is substituted by hydroxyl groups. You further related these difference to the toxicological behaviour of the target and source substances.

In particular, you referred to the data on acute toxicity, irritation/corrosion and sensitization for the source and target substance. However, it is unclear how a comparison of these properties supports the assumption of similar reproductive toxicity potential in particular in the absence of any data on fertility for the registered substance.

You pointed out that testing with cyanuric chloride is difficult due to the rapid hydrolysis of cyanuric chloride in contact with water and the formation of hydrochloric acid which causes corrosive effects. These local effects would then cause secondary responses that confound the interpretation of the study. You should be reminded that in vivo testing with corrosive substances at concentration/ dose levels causing corrosivity shall be avoided.

For the endpoints of EOGRTS and second-species PNDT, you did not provide the robust study summary of the study information that is to be read-across, but made reference to the information via a web link. ECHA has not assessed this information since it is not present in the Registrant's comment, and so ECHA is unable to determine whether these studies would be compliant with the requirements of Annex XI, 1.5. In particular, ECHA notes that a "*three-generation reproduction toxicity study*" does not correspond to the test specified in the information requirement, and that the use of such a study would need justification.

In conclusion, ECHA is of the opinion that the testing of cyanuric acid would not be representative of the registered substance as the hydrolysis half-lives do not exclude bioavailability to the intermediate hydrolysis products. Consequently, on the basis of the information available there is not an adequate basis for predicting the properties of the registered substance. Therefore, the read-across cannot be accepted.

The information provided 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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015).

In your comments to the draft decision you proposed to change the study design with regard to the premating period and the animal cohorts in the extended one-generation study. You state that "*A 10 weeks premating period exceeds the standard requirements stated in the OECD Guideline and the registrant insists to limit the premating exposure to 14 days, also considering animal welfare reasons, as a longer exposure/treatment also mean a prolonged stress to the animals.*
If a 10 weeks premating period is nevertheless requested, it should be limited to the male animals and start dosing the female animals two weeks premating as requested by the OECD Guideline again for animal welfare reasons."

With regard to the premating time, as specified in ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015), Appendix R.7.6–3, " *If the registrant applies ten weeks premating exposure duration in an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) no justification for premating exposure duration is needed. Substance specific justifications should be provided substantiated with data if shorter than ten weeks premating exposure duration is proposed.*" ECHA considers there are no substance specific reasons to deviate from the 10 weeks premating period.

In your comments to the draft decision, you also proposed to limit the test cohorts to cohort 1A only. In relation to this you are reminded that cohort 1B t is a standard requirement and as such cannot be waived.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

It is recommended that results from a range-finding study (or range finding studies) for the extended one-generation reproductive toxicity study are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

2. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, your technical dossier for the registration of your substance at a tonnage of more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral (gavage) route using the registered substance as test material.With regard to the testing in a second species, you have sought to adapt this information requirement generically according to Annex XI, Section 1. You provided the following justification for the adaptation:

"According to Regulation (EC) No.1907/2006, Annex XI, 1., standard data requirements can be adapted in case testing does not appear scientifically necessary.

For the endpoint pre-natal developmental toxicity a GLP and guideline compliant study is available. In this study no differences in the incidence of fetal malformations and developmental variations between control and treated groups were observed. From the entire toxicological data set it can be concluded that local effects are the predominant effects of Cyanuric chloride via the most relevant exposure route inhalation.

In the subchronic inhalation toxicity study (94-0211-DKT) a true systemic NOAEC could not be established since no adverse systemic effects were noted. Also in a repeated dose dermal toxicity study (83-0093-FKT) effects were only seen at the portal of entry due to the irritation and caustic effects of Cyanuric chloride.

In human studies ([redacted] 1971 and 1965; [redacted] 1998; [redacted], 1984) local effects due to irritating/caustic nature of Cyanuric chloride occurred whereas no systemic effects related to test item treatment were seen. Taking into account the absence of systemic effects in animal and human studies as well as the clearly negative outcome of the pre-natal developmental toxicity in the first species, the registrant is of the opinion that the repetition of the pre-natal developmental toxicity in a second species would not provide any new knowledge for this substance, also considering the aspect of animal welfare."

While you have not explicitly claimed a specific adaptation under Section 1 of Annex XI, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2. In your justification you refer to data from a pre-natal developmental toxicity study in rats showing no developmental toxicity effects in this species. You also used as an argument in your justification the data provided for other endpoints in the dossier such as repeated dose studies, dermal toxicity and human studies indicating that the registered substance induces mainly local effects, but arguing that there are no systemic effects.

However, ECHA notes that in your justification to adapt the Annex X, Section 8.7.3 information requirement you state that: "*The teratogenicity/pre-natal developmental toxicity study according to OECD 414 (83-0091-FGT) indicated adverse effects on embryo/fetal development only in combination with severe maternal toxicity.*" This suggests that the registered substance is systemically available and may cause developmental toxicity.

You also consider that: "*From the entire toxicological data set it can be concluded that local effects are the predominant effects of Cyanuric chloride via the most relevant exposure route inhalation.*"

For the reproductive toxicity endpoints identification of intrinsic hazardous properties of the substance is important. To maximize the internal dose for hazard identification, the oral route is usually preferred if the substance is a solid or liquid. You have not provided a justification why the oral route is irrelevant for your substance to investigate the prenatal developmental toxicity and you regard the results of the existing studies via the oral route as relevant.

Furthermore, ECHA notes that there is a variety of evidence in the dossier that the registered substance induces systemic effects. For example, in the provided human studies, alteration of the visco elastic properties of the arterial vessels of the workers of a cyanuric chloride producing plant ([redacted] 1998), and symptoms related to impaired health ([redacted] 1971; [redacted] 1984) were reported, and in the repeated dose toxicity section (see Appendex 1, section 3 below), systemic effects are reported after oral or inhalation exposure.

Hence ECHA considers that the assertion that there are no systemic effects of the registered substance is contradicted by the data in the dossier. Consequently ECHA considers that the hypothesis (that the prenatal developmental toxicity effects generally and on a second species can be excluded because of an absence of systemic effects (and hence exposure)) via inhalation or oral route is not supported by the data and not an adequate basis to assume/conclude on the prenatal developmental toxicity properties of the registered substance.

Regarding the results from the existing prenatal developmental toxicity study, and given that there is systemic availability of the registered substance and systemic effects, ECHA considers it is not possible to assume / conclude only based on the available information that the registered substance is not a developmental toxicant.

ECHA therefore concludes that your adaptation does not meet the general rules for adaptation of Annex XI, Section 1.2., because it is not possible to assume/conclude based on the information if the registered substance has not a hazardous property on pre-natal developmental toxicity.

Therefore, your adaptation of the information requirement is rejected.

Upon the submission of the draft decision you submitted comments and proposed to use read-across to adapt the standard information requirements (REACH Annex X, section 8.7.3 and Annex X, section 8.7.2), in accordance with the provisions of Annex XI, 1.5 of the REACH Regulation. However, as explained in section 1 of Appendix 1, the proposed adaptation cannot be accepted as the information now stands.

As explained above, the information provided 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.

The test in the first species was carried out by using a rodent species (rats). According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are 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 TG 414) in a second species rabbits by the oral route.

3. Classification and labelling (Annex VI, Section 4.)

Pursuant to Article 10(a)(iv) of the REACH Regulation your technical dossier shall contain information on classification and labelling of the substance as specified in Annex VI, Section 4 of the REACH Regulation in conjunction with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation).

Annex VI, section 4.1. clarifies that the hazard classification of the substance shall result from the application of Title I and II of the CLP Regulation. In addition, for each entry, the scientifically justified reasons why no classification is given for a hazard class or differentiation of a hazard class should be provided. According to Article 5(1) of Title I of the CLP Regulation, a substance shall be classified on the basis of available information.

Furthermore, the technical dossier must include the resulting hazard label for the substance in line with Title III of the CLP Regulation (Annex VI, section 4.2 of the REACH Regulation).

For repeat-dose toxicity (oral route), you have provided an OECD TG 407 study (Jedrychowski, 1992), in which the registered substance killed animals at multiple doses below 100 mg/kg/day down to a dose of 4 mg/kg, where 10% of the females died. Dose dependent histopathological lesions were present in the gastro-intestinal tract, liver, spleen and lung. According to Annex I, Section 3.9. of Regulation (EC) No. 1272/2008, the guidance value for significant toxic effects by the oral route is 100 mg/kg/day for a 90-day study. ECHA notes that significant toxic effects are seen at levels below the guidance value for classification for Specific Target Organ Toxicity- Repeated Exposure by the oral route.

For repeat-dose toxicity (inhalation route), you have provided a 90-day study (NOAEC at maximum concentration of 0.25 mg/m^3), a 28-day study (maximum concentration of 1.5 mg/m^3 with effects on lymph node weight), a supporting 5 month study (Blagodatin, 1968), the registered substance was tested at 1.88 mg/m^3 with effects such as "tracheaitis, bronchitis, peribronchitis, interstitial pneumonia, liver dystrophy, myocardial dystrophy, kidney dystrophy". According to Annex I, Section 3.9. of Regulation (EC) No. 1272/2008, the guidance value for significant toxic effects by the inhalation route is 1 mg/l/6h/day (or 1 g/m^3/6h/day) for a 90-day study. ECHA notes that significant toxic effects are seen at levels multiple orders of magnitude below the guidance value for classification for Specific Target Organ Toxicity- Repeated Exposure by the inhalation route.

The dossier does not contain any justification for non-classification but just the statement "*Based on the available data Cyanuric chloride is not subject for C&L regarding repeated dose or specific target organ toxicity according to Directive 67/548/EEC and Regulation (EC) No 1272/2008.*"

Upon the submission of the draft decision you submitted comments in which you disagreed on classification of the substance as STOT-RE. You argue that "*The data source addressed by ECHA is available as an abstract only and, thus, rated as Klimisch code 4. Furthermore, the overall repeated dose data set has to be taken into account, especially with regard to the reproducibility of effects noted in potential target organs identified. For repeated oral exposure there is further experimental data available in form of a 5-day oral toxicity study in the rat (94-0211-DKT [1]). In this study the clinical signs reported (excessive salivation, laboured breathing, gasping, decreased motor activity, brown material around mouth/nose etc.) need to be considered in context with the corrosive properties of the test material.*"

You also explained that "*The affected organs mentioned in the abstract published by Jedrychowski [9] were not confirmed in this study with the exception of the gastro-intestinal tract, which is in agreement with the corrosive properties. The registrant is of the opinion that the intention of classification and labelling with STOT-RE (oral) is to take into account severe systemic toxicity with explicit target organ susceptibility.*

Based on these considerations, the registrant is of the opinion that classification and labelling of cyanuric chloride based on reported local effects due to corrosive properties lacking an organ specificity based on an abstract is not appropriate." and that "*This effect is local and already occurs after single inhalation exposure to the substance.*

Although the mode of action is corrosivity, classification and labelling of cyanuric chloride with acute inhalation toxicity category 2 (H330) has been assigned. Furthermore, the substance is classified/labelled with STOT-SE cat. 3 (H335) to account for the irritation potential."

ECHA notes that the Guidance on the Application of Regulation (EC) No 1272/2008, specifies in Section 3.9.2.4. that "*Reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect demonstrates support for the classification.*" Further, the Guidance states "*Where a number of studies are available these should be assessed using a weight of evidence approach to determine the most appropriate classification.*" ECHA considers this is the appropriate way to evaluate the evidence. ECHA acknowledges the limitations to the reliability of the studies, as exemplified by the Klimisch scores. Nonetheless, ECHA takes the view that the consistency of evidence is strong, as described in the following paragraphs.

For the inhalation route, ECHA notes the reliable OECD 413 study that shows no systemic toxicity up to 0.25 mg/m^3, and that your dossier states that 0.05 mg/m3 is a NOAEC for "local effects in the lung due to the corrosive action of cyanuric chloride". Therefore 0.25 mg/m3 is a LOAEC for local effects, i.e. ~1000-fold below the guidance value for classification as STOT-RE1. This is a comparable LOAEL with the 28-day study of Rydzynski et al. 1993 showing toxic effects at 0.2, 0.4, 1, 1.5 mg/m^3. Blagodatin 1968 report a variety of effects, including death, at a dose level of 1.88 mg/m3 (i.e. ~100-fold below the guidance value for classification as STOT-RE1) when exposure was extended to 2.5 months.

For the oral route the evidence of toxicity comes also from a 28-dat study available only as an abstract (Jedrychovski et al. 1992), where all the doses (down to the lowest of 4 mg/kg) induced mortality. Note that the guidance value for classification as STOT-RE1 is 10 mg/kg/day for a 90-day study, and 30 mg/kg/day for a 28-day study. Thus, there is severe toxicity at values ~9-fold below the guidance value. A reliable 5-day dose range finding study (83-0090-FKR) found stomach lesions due to corrosion at 20 mg/kg/day and above, and death at 40 mg/kg/day and above. The guidance value for classification as STOT-RE2 is 100 mg/kg/day for a 90-day study

ECHA notes that 'morbidity or death resulting from repeated or long-term exposure' is specifically mentioned in the ECHA CLP guidance as an example of severe toxicity.

ECHA agrees with your quotation of CLP Guidance, "*Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure.*" ECHA notes that you reported an oral LD50 of 333.6 mg/kg, and an inhalation LD50 of 170 mg/m3. These LD50 values are ~90 and ~80-fold above the concentrations that cause death in repeated-dose studies.

According to Section 3.9.2.5.1 of the Guidance, on "Irritating/corrosive substances", "*One way to distinguish between these possibilities is to consider the dose level which causes the toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity. In this case, classification as specific target organ toxicant (repeated exposure) would be warranted even if the substance (or mixture) is also classified as acutely toxic and/or corrosive.*"

As explained above, the registered substance causes significant toxic effects at repeated dose levels below the Guidance values for classification for STOT-RE and there is not sufficient justification for non-classification.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit information on the classification and labelling of the registered substance subject to the present decision. In the alternative, the Registrant is required to provide the scientifically justified reasons why no such classification is given. The Registrant is reminded that also for a differentiation of a hazard class, scientifically justified reasons need to be provided.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 36 months. You sought to justify this request stating: "*The registrant would propose to extend the deadline from 30 to 36 months. This is because dose-range finding test(s) for the OECD TG 414 study in rabbits have to be done and besides that, the capacity of laboratories carrying out such tests is limited already due to the recent requests by ECHA for these types of studies after a long waiting period and, thus, it is not predictable when the extended one-generation study can start*". However, ECHA points out that this timeline was already set to include a dose-range finding study. In addition, the argument on the limited capacity of the laboratory to perform the test within the set timeline needs to be supported by adequate documentation (e.g. proof from the laboratory that is going to perform the test that this is the case). You were invited to provide this supporting evidence by 28 October 2016; however, no evidence was provided. Therefore, ECHA has not modified the deadline of the decision.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

The compliance check was initiated on 19 November 2015.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-52 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2017.

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

3. 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 your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported 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 the substance tested in the new test(s) 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 or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) 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 test(s) to be assessed.