EUROPEAN CHEMICALS AGENCY

Helsinki, 10 May 2016

Addressee: [redacted]

Decision number: TPE-D-2114328818-39-01/F
Substance name: TIPX
EC number: 457-670-6
CAS number: 157859-20-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17 July 2015

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

Your testing proposal is accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**
2. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) using the pre-hydrolysed sample of the registered substance.**

Your testing proposal is modified and you are requested to carry out:

3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy using the registered substance.**

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 **17 May 2018**. 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

[For the final decision: 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.**]**

[For the final decision: Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3**]**

[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

The decision of ECHA is based on the examination of the testing proposals submitted by you.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD TG 414.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You did not specify the species to be used for testing. According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

You did not specify the route for testing. 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 4.0, July 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31/OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6.2.3.2 (July 2015).

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.
"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for testing the pre-hydrolysed sample of the registered substance triisopropylsilylacrylate for long-term toxicity on aquatic invertebrates [*Daphnia magna* reproduction test, EU C.20/OECD TG 211/] with the following justification:

"2-Propenoic acid, tris(1-methylethyl)silyl ester hydrolyses very rapidly in solution. The silanol hydrolysis product has low solubility in water and relatively high log Kow. The limiting concentration in water is low due to expected tendency to dimerise in solution. Some aquatic toxicity is to be expected and it is possible that short term testing may not have fully captured the potential for chronic effects.
Therefore, new testing of long-term toxicity to aquatic invertebrates is proposed for a prehydrolysed sample of the registration substance.
A 21-day NOEC (maternal toxicity) of 7 mg/l (measured) for the non-silicon containing hydrolysis product, acrylic acid (CAS 79-10-7) from a semi-static test is reported in the EU Risk Assessment Report (EC, 2002). The 21-day NOEC (reproductive effects) was 12 mg/l (measured) in the same test."

ECHA understands that in this case you are proposing to conduct the long-term aquatic toxicity test with the pre-hydrolysed sample of the registered substance because, due to rapid hydrolysis, it is expected that the outcome of the test would be the same as the outcome of the test conducted with the registered substance.

ECHA notes that the registration dossier contains data showing that the registered substance will hydrolyse rapidly with a half-life significantly less than one hour and that two hydrolytical degradation products, tris(1-methylethyl)silanol and acrylic acid, are formed. ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R.7b, Table R. 7.8-3 indicates that where degradation is rapid (e.g. half-life < 1hour), the available test data will define the hazard of the degradation products since it will be these that have been tested. These data may be used to classify the parent substance in the normal way. Furthermore, according to OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 the aquatic toxicity of degradation products may be determined by allowing the parent compound to degrade and then exposing the test organisms to the resulting media. More specifically, OECD (2000)6 suggests to test degradation products when degradation half-life is less than 1 hour.

Furthermore, ECHA notes that testing with the pre-hydrolysed sample is in line with the aquatic toxicity data already available in the dossier because the data are based on the exposure to the test solutions, where hydrolytical degradation products have been allowed to form before the introduction of the test organisms in the resulting test media. Accordingly, all aquatic toxicity effect values reported in the dossier are based on analysed concentrations of the hydrolytical degradation product tris(1-methylethyl)silanol.

Based on the above, ECHA considers that in this case testing the long-term exposure to hydrolytical degradation products of the registered substance rather than the registered substance itself is relevant in order to generate the required information on the registered substance and, accordingly, testing with the pre-hydrolysed sample as you proposed is deemed appropriate. Therefore, ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH regulation.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R.7b (section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity fish or invertebrates is shown to be substantially more sensitive than the other, a long-term study on the more sensitive species is required. ECHA notes that based on the short-term data in the registration dossier, aquatic invertebrates are substantially more sensitive than fish.

Therefore, pursuant to Article 40(3)(a)of the REACH Regulation, you are requested to carry out the proposed test using the prehydrolysed sample of the registered substance (triisopropylsilylacrylate) subject to the present decision: *Daphnia magna* reproduction test (test method: EU C.20/OECD TG 211).

Notes for your consideration

Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, you shall submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6. If you come to the conclusion that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6. taking into account the new data generated by the *Daphnia* study requested by the present decision.

Due to the rapid hydrolysis of the substance you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance, Chapter R.7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances mentioned above for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

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

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) by the oral route according to EU B.26/OECD TG 408.

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, July 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. Even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route are low (below [redacted] mg/m3). Hence, the oral route remains the most appropriate route and the test shall be performed by the oral route using the test method EU B.26/OECD TG 408.

You did not specify the species to be used for testing. According to the test method EU B.26/OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In the 28 day repeated dose toxicity study present in your registration dossier histopathological changes such as renal tubular necrosis accompanied by tubular basophilia and hyaline droplets, increased kidney weights, and increase in creatinine kinase and phospholipids were observed in male rats. The fact that these effects were only observed in male rats indicates that the registered substance may induce alpha-2µ-globulin-mediated nephropathy. Since humans do not excrete alpha-2µ-globulin, this mode of action is not relevant to humans. For this reason, ECHA decides to include in the request for a sub-chronic toxicity study urinalysis (which is optional in paragraph 30 of OECD TG 408, and the relevant part of Section 1.5.2.2. of EU Method B.26) to investigate kidney function, and a full histopathological examination (paragraph 36 of OECD TG 408, Section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2µ globulin.

Thus, in accordance with Article 13(3) of the REACH Regulation, ECHA considers that the sub-chronic toxicity study (90 day) by the oral route according to EU B.26/OECD TG 408 if modified as explained above is appropriate to address the standard information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD TG 408) modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2µ globulin nephropathy.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 17 July 2015.

ECHA held a third party consultation for the testing proposals from 30 August 2015 until 15 October 2015. ECHA did not receive information from third parties.

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

ECHA notified you of the draft decision and invited you to provide comments. ECHA did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. 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 eventually result in a notification to the Enforcement Authorities of the Member States.

3. 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.