ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 01 September 2016

Addressee [redacted]

Decision number: TPE-D-2114340400-68-01/F
Substance name: Quaternary ammonium compounds, bis(hydrogenated tallow alkyl)dimethyl, chlorides, reaction products with polyethylenepolyamines and tall-oil fatty acids, humates hydrochlorides
EC number: 272-745-1
CAS number: 68910-55-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05.05.2014

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 proposals are accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats using the registered substance using nose-only exposure and including bronchoalveolar lavage (BAL) analysis.**
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 registered substance.**
3. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) using the registered substance.**

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

4. **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.**

Your following testing proposal is rejected:

5. **Reproductive toxicity study (Annex IX, Section 8.7.3.)**

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 **8 March 2019**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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[2] by Claudio Carlon, Head of Unit, Evaluation E2

[2] 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 and scientific information submitted by third parties.

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

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

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) in rats by the inhalation route according to OECD TG 413 to be performed with the registered substance.

You proposed testing by the inhalation route. The registered substance is reported to be a solid powder with a high molecular weight (i.e. >20000 Da) and a low water solubility (i.e. 0.054 mg/L). The uses reported for the substance can generate aerosols, particles or droplets of an inhalable size. In addition, inhalation toxicity studies provided in the registration dossier indicate a concern for toxicity (e.g. bronchiolo-alveolar hyperplasia) that should be investigated further. Therefore, ECHA agrees that the inhalation route is the most appropriate route of administration for testing.

The registered substance is a dust that is highly insoluble in water. The results of the particle size distribution provided in the registration dossier indicate that approximately 3 % (by mass) of particles are less than 10 µm. Since the available data on the substance solubility in water and particle size distribution indicate that the lower respiratory tract (i.e., the alveoli) might be the primary site of deposition and retention of the registered substance subject to the present decision and no information is yet available to characterize the risk, ECHA requests that bronchoalveolar lavage (BAL) is performed in the test. BAL fluid shall be analyzed for total and differential cell count, protein content and lactate dehydrogenase. You should consider to investigate further parameters taking into account potential effects the substance may exhibit in the lung. You should further consider that the preferred mode of exposure is nose-only and that particulate materials should be subjected to mechanical processes. Particle sizing should be performed for all aerosols and for vapours that may condense to form aerosols. To allow for exposure of all relevant regions of the respiratory tract, aerosols with mass median aerodynamic diameters (MMAD) ranging from 1 to 3 µm with a geometric standard deviation (σg) in the range of 1.5 to 3.0 are recommended.

You proposed testing in rats. According to the test method OECD TG 413 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 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: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD TG 413).

The test shall be performed using nose-only exposure and shall include bronchoalveolar lavage (BAL) analysis.

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 proposal for testing the registered substance for long-term toxicity on aquatic invertebrates *Daphnia magna* reproduction test, EU C.20/OECD TG 211 with the following justification: "*In accordance with Annex IX, Section 9.1.5, a long-term aquatic invertebrate toxicity test will be conducted based on organolignite's poor solubility in water (54 µg/L). A chronic, long-term (i.e., 21-day) exposure provides a better indication of potential toxicity to the test substance than a shorter duration (i.e., 48-hour), acute test. The study protocol will meet the technical requirements of OECD 211 (21-day, reproduction study), and the study will be undertaken at a GLP compliant laboratory.*" ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed test using the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (test method: *Daphnia magna* reproduction test, 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.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance, Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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 fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. 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 proposal for testing the registered substance for long-term toxicity on fish (Fish, early-life stage toxicity test, OECD TG 210) with the following justification: "*In accordance with Annex IX, Section 9.1.6, a long-term fish toxicity test will be conducted based on organolignite's poor solubility in water (54 µg/L). A chronic, long-term (i.e., 28 d) exposure provides a better indication of potential toxicity to the test substance than a shorter duration (i.e., 96 h), acute test. The study protocol will meet the technical requirements of OECD 210 (28 -days post-hatch, fish early life stage study), and the test itself will be GLP compliant.*" ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.6 of the REACH regulation.

Therefore, pursuant to Article 40(3)(a)of the REACH Regulation, you are requested to carry out the proposed test using the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: Fish, early-life stage toxicity test, OECD TG 210).

Notes for your consideration

Once results of the proposed test on long-term toxicity to fish are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance, Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

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

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) Examination of the testing proposal

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 in rats according to EU B.31/OECD TG 414 by the inhalation route.

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

You proposed testing with rats. 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 proposed testing by the inhalation route. The registered substance is reported to be a solid powder with a high molecular weight (i.e. >20000 Da) and a low water solubility (i.e. 0.054 mg/L). 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. For the registered substance exposure by the oral route provides a higher possibility of systemic availability because higher doses can be administered. Hence, ECHA concludes that testing should be performed by the oral route.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has indicated that based on physicochemical properties the substance is predicted to be not absorbed in the gastrointestinal tract and to have a low inhalation potential, and that the substance displays a low toxicity profile.

ECHA notes that it is the Registrant's responsibility to consider and justify in the registration dossier any adaptation of the information requirements in accordance with Annex IX, Section 8.7., column 2, third indent. This adaptation specifies that a pre-natal developmental toxicity study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.*" ECHA notes that all three criteria need to be met.

ECHA observes that the third party comment addressed only the criteria concerning absorption, low inhalation risk and the lack of evidence of toxicity. However, the third party did not provide factual evidence that no systemic absorption occurs via any relevant route of exposure. Furthermore, an adaptation would also need to demonstrate that there is no or no significant human exposure.

Therefore the criteria listed in column 2 of Annex IX, Section 8.7., third indent are not met and the information requirement for the pre-natal developmental toxicity study cannot be adapted on this basis.

c) Outcome

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: 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).

5. Reproductive toxicity study (Annex IX, Section 8.7.3.)

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

a) Examination of the testing proposal

You have submitted a testing proposal for a two-generation reproductive toxicity study according to EU B.35/OECD TG 416.

According to Annex IX, Section 8.7.3., as amended by Commission Regulation (EU) 2015/282 (entered into force on 13 March 2015), a two-generation reproductive toxicity study is no information requirement any longer. However, the requirement according to Annex IX, Section 8.7.3., i.e. the extended one-generation reproductive toxicity study, is only an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD TG 421 or 422 screening studies) or if they reveal other concerns in relation with reproductive toxicity.

ECHA notes that there are results of a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) available in the registration dossier that did not indicate adverse effects on reproductive organs or tissues or reveals other concerns in relation with reproductive toxicity.

ECHA notes further that you have not included any justification why to perform a reproductive toxicity study at tonnage level 100 – 1000 tonnes per year. ECHA considers that the proposed study is at this stage not necessary to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation because no adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity have been observed in repeated dose toxicity study.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

A third party has indicated that the tonnage level of the registered substance only requires the conduct of a two-generation reproduction toxicity study if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues. For the same reason ECHA rejects this testing proposal for a two-generation reproductive toxicity study.

As the extended one-generation reproductive toxicity study is not triggered, the adaptation proposed by the third party does not need to be assessed.

c) Outcome

ECHA concludes that at this stage there is no information gap for the information requirement of Annex IX, Section 8.7.3. Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the proposed two-generation reproduction toxicity study (OECD TG 416) is rejected.

d) *Notes for your consideration*

Once the results from the sub-chronic toxicity study (Appendix 1, 1. above) are available, you should reconsider the information requirement of Annex IX, Section 8.7.3. If the sub-chronic toxicity study indicates adverse effects on reproductive organs or tissues, or reveals other concerns in relation with reproductive toxicity, a new testing proposal for the present endpoint would – in accordance with the REACH Regulation – have to be submitted, unless compliance with this information requirement is scientifically justified and documented by means of specific or general rules of adaptation.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination pursuant to Article 40(1) on 5 May 2014.

ECHA held a third party consultation for the testing proposals from 23 January 2015 until 9 March 2015. ECHA received information from third parties (see Appendix 1).

On 9 December 2015 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 1 February 2016 the Registrant did not provide any comments on the draft decision to ECHA.

This decision does not take into account any updates after **2 March 2016**, 30 calendar days after the end of the commenting period.

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 on 9 December 2015 and invited you to provide comments.

You did not comment on the draft decision by 2 February 2016.

On 3 March 2016, ECHA notified the competent authorities of the Member States of its draft decision and invited them to propose amendment to the draft decision under Article 51 of the REACH Regulation. Subsequently, amendment to the draft decision was proposed.

The ECHA Secretariat reviewed the proposed amendments and did not amend the draft decision. ECHA referred the draft decision to the Member State Committee on 18 April 2016.

ECHA invited you to comment on the proposed amendments on 8 April 2016.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-48 meeting and ECHA took the decision according to Article 51(6) 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 requests in this decision, or to fulfil otherwise the information requirements with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In carrying out the tests 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 tests 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 tests to be assessed.