EUROPEAN CHEMICALS AGENCY

Helsinki, 19 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114350930-53-01/F
Substance name: Quaternary ammonium compounds, tri-C8-10-alkylmethyl, chlorides
EC number: 264-120-7
CAS RN: 63393-96-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15 December 2015
Registered tonnage band: 1-10 tonnes per annum

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

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that both studies requested under 1. and 2. have negative results;**

4. **Short-term repeated dose toxicity study (28 days), (Annex VIII, Section 8.6.1.; test method: EU B.7./OECD TG 407) in rats, oral route with the registered substance;**

5. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421 or 422) in rats, oral route with the registered substance; and**

6. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) with 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 **26 June 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[1] by Leena Ylä-Mononen, Director of Evaluation

[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

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have adapted the standard information requirements for:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.),
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.),
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.),
- Short-term repeated dose toxicity study (28 days) (Annex VIII, Section 8.6.1.), and
- Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and property-specific context.

0.1. Introduction of the grouping and read-across approach proposed by the Registrant

You provided a read-across justification document in section 13 of the IUCLID registration dossier. With respect to the selection of source substances for the provided read-across, you stated that "*with regard to monomethylated compounds, no toxicological data were available" and "substances were considered for read-across if they contained one or two methyl groups.*" Your justification is based on the following considerations: Structural similarity because all substances are quaternary ammonium compounds; similar molecular weights of 360-590 Da; comparable physicochemical properties; similar toxicological properties with respect to irritation/ corrosion; classification of some of the substances as acute toxic; local irritation and general systemic effects prevail in repeated dose and reproductive toxicity studies with similar NOAELs; substances do not exert specific reproductive effects; and there is no indication of genetic toxicity. Additionally, for repeated dose toxicity, you proposed a worst-case approach by reading across the data of the provided 28-day study with the source substance CAS RN 107-64-2 and using the corresponding NOAEL for DNEL derivation.

ECHA understands that these arguments comprise your hypothesis, and it is on this basis that you propose that the human health properties of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

With respect to genetic toxicity *in vitro*, you provided the following studies in order to fulfil the REACH requirements of Annex VII, Section 8.4.1. and Annex VIII, Sections 8.4.2. and 8.4.3.:

- Zeiger 1992 (publication): Study equivalent or similar to OECD 471 (Bacterial Reverse Mutation Assay) using the source substance CAS RN 68783-78-8 ($R_{1,2}$ = methyl, $R_{3,4}$ = tallow fatty acids (mainly C16-18 even numbered, and C18-unsaturated)), reliability 2 (deviations: no *E.coli* WP2 strain or TA102 tested, only 2-Aminoanthracene as positive control with S9 mix);
- Inoue 1980a (publication): Study equivalent or similar to OECD 471 (bacterial reverse mutation assay) using the source substance CAS RN 7173-51-5 ($R_{1,2}$ = methyl, $R_{3,4}$ = C10), reliability 2 (deviations: only strains TA98 and TA100 tested);
- [redacted] 2002: Study according to EU B.10 (mutagenicity - *in vitro* mammalian chromosome aberration test) using the source substance CAS RN 61789-80-8 (dimethyldioctadecylammonium chloride), reliability 2; and
- Inoue 1980b (publication): Study equivalent or similar to EU B.21 (*in vitro* mammalian cell transformation test) using the source substance CAS RN 7173-51-5 ($R_{1,2}$ = methyl, $R_{3,4}$ = C10), reliability 2.

With respect to repeated dose toxicity, you provided four studies (one 28-day, two 90-day and one 17-week studies) in order to fulfil the REACH requirement of Annex VIII, Section 8.6.1.:

- ECB 2002 (publication): Study equivalent or similar to OECD 407 (repeated dose 28-day oral toxicity in rodents) using the source substance CAS RN 107-64-2 ($R_{1,2}$ = methyl, $R_{3,4}$ = stearyl), reliability 2;
- USA EHA-MT 1970 (review article/handbook): Study equivalent or similar to OECD 408 (repeated dose 90-day oral toxicity in rodents) using the source substance CAS RN 7173-51-5 ($R_{1,2}$ = methyl, $R_{3,4}$ = C10), reliability 2;
- [redacted] 1977 (study report): Study equivalent or similar to OECD 409 (repeated dose 90-day oral toxicity in non-rodents) using the substance CAS RN 26062-79-3 ($R_{1,2}$ = methyl, $R_{3,4}$ = propenyl), reliability 2 (this study record is not used for read-across but as supporting information); and
- BIBRA 1987 (secondary source)/Cutler and Drobeck 1970 (publication): Study equivalent or similar to OECD 408 (repeated dose 90-day oral toxicity in rodents) using the source substance CAS RN 61789-77-3 ($R_{1,2}$ = methyl, $R_{3,4}$ = coco fatty acids (mainly C12-C14), reliability 4.

With respect to reproductive toxicity, you provided the following study in order to fulfil the REACH requirement of Annex VIII, Section 8.7.1.:

- ECB 2002 (publication): Study according to OECD 421 (reproduction / developmental toxicity screening test) using the source substance CAS RN 107-64-2 ($R_{1,2}$ = methyl, $R_{3,4}$ = stearyl);
- Inoue 1980c (publication): Non-GLP/non-guideline study using the source substance CAS RN 1812-53-9 ($R_{1,2}$ = methyl, $R_{3,4}$ = C16), reliability 2; and
- Palmer 1983 (publication): Non-GLP/non-guideline study using the source substance CAS RN 107-64-2 ($R_{1,2}$ = methyl, $R_{3,4}$ = stearyl), reliability 4.

Based on your read-across justification, ECHA concludes that your read-across hypothesis is that source and target substances exert similar toxicological properties and/or that source substance CAS RN 107-64-2 is the worst case for repeated-dose toxicity, and it is this basis which allows you to read-across the properties of source substances directly to the registered substance.

0.2. ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, Section 1.5.

ECHA has the following observations:

i. The substance characterisation for the source studies needs to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities of the source substances used in each study. In the ECHA practical guide "How to report on Read-Across" it is recommended to follow the Guidance on identification and naming of substances und REACH (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

   ECHA observes that the documentation of the source substances for the proposed read-across is very limited (see 0.1 above). The source substances are identified by their CAS RN and chemical structures. However, in all read-across studies except ECB 2002 (28-day repeated dose toxicity study) and EU RAR 2002 (*in vitro* mammalian chromosome aberration test), the impurity profiles of the source substances cannot be assessed using the information provided in the registration dossier and, hence, ECHA cannot verify what chemical compounds are present. Therefore, as the structural similarity between the source substances and the target substance cannot be established, prediction of toxicological properties is not possible.

ii. Your read-across justification relies upon the structural similarity of the source and the registered substance. Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general that structural similarity per se is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. Hence, further elements are needed such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks. ECHA considers that the requirement of Annex XI, section 1.5, that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach), has not been met.

iii. To support your read-across, you provided a comparison of physicochemical properties of source and target substances including melting point, boiling point, vapour pressure, water solubility, partition coefficient, lipophilic character and molecular weight. For example, you stated that "*the molecular weight ranges between 360-590 Da*"; "*it is more likely that all substances decompose at temperatures around 140-160 °C*"; "*substances with C16-C18 fatty acids are practically insoluble in water, whereas those with C8-C10 chain lengths [...] are at least partly soluble*"; "*with regard to the log Kow, the tested or predicted values for all substances are ≥ 4.66*"; and "*it is assumed that the lipophilic character as well as the similar molecular weight determines the toxicokinetic behavior.*" However, you did not explain how this information can be used to predict the

properties under consideration. In particular, it is unclear how your comparison of physicochemical properties supports read-across of in vitro genotoxicity, repeated dose toxicity, reproduction / developmental toxicity screening and pre-natal developmental toxicity. While similar physicochemical properties are common when applying the grouping and read-across approach, ECHA does not accept in general that similar physicochemical properties per se are sufficient to enable the prediction of human health properties of a substance, since similar physico-chemical properties do not always lead to predictable or similar human health properties.

iv. Furthermore, your proposed read-across is based on similar toxicological properties, including acute toxicity and irritation/corrosion, the effect levels and similar effects in repeated-dose and reproductive toxicity studies, similarity in genetic toxicity, and classification of some of the substances as acute toxic. However, you did not explain how this information can be used to predict the properties under consideration. ECHA considers that while similar toxicological properties are common when applying the grouping and read-across approach, ECHA does not accept in general that similar toxicological properties per se are sufficient to enable the prediction of all human health properties of a substance, since similar toxicological properties for some endpoints do not always lead to predictable or similar human health properties for the remaining human health endpoints.

v. You have provided a comparison of three repeated dose toxicity studies: (1) A 28-day study in rats with the source substance CAS RN 107-64-2 (reliability 2); (2) a 90-day study in rats with the source substance CAS RN 7173-51-5 (reliability 2); and (3) a 90-day study in rats using the source substance CAS RN 61789-77-3 (reliability 4). ECHA notes that in study (1) the NOAEL is based on kidney effects (adrenal weights significantly increased, combined with histopathological changes). In comparison, no kidney effects were observed in studies (2) and (3). The NOAEL in study (2) is based on unspecific effects (increased caecum to body weight ratio; decreased body weight gain) and no adverse effects were observed in study (3). ECHA notes that the provided repeated dose toxicity studies with three different source substances resulted in significantly different toxicological effects.

   Thus the structural differences between these substances seem to have significant impact on toxicological properties for the proposed set of source substances, and it seems that the source substances act through different mechanisms. This finding contradicts the Registrant's hypothesis of similar toxicological effects of target and source substances, and consequently undermines predictions based on this hypothesis.

vi. For the read-across of repeated-dose toxicity, you proposed a worst-case approach: "*The NOAEL derived from the study substance 2 is used as starting point for the DNEL derivation. This worst case approach considers the rat as most sensitive species as well as the fact that the lowest NOAEL is obtained from this study (if study duration is considered).*" However, you have not set out clearly why this study should constitute a worst case approach; for example, you have not explained the structural feature(s) that control toxicity and the magnitude of the differences in toxicity. ECHA considers that in view of the different effects exerted by the structurally different source substances, it cannot be excluded that also the target substance exerts significantly different toxicological effects; i.e. it might be even more potent. ECHA also notes that the hypothesis of the worst-case approach contradicts your hypothesis that the substances have similar toxicological properties, and that these differing approaches are not reconciled in

your read-across justification. ECHA concludes that the worst-case hypothesis is not an adequate basis to predict the toxicological properties of the registered substance.

vii. Annex XI, Section 1.1.2 (2) and Annex XI, Section 1.5 require for non-GLP studies and studies used for read-across purposes that "*adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)*".

- With respect to REACH requirement Annex VII, Section 8.4.1., *in vitro* gene mutation study in bacteria, you provided endpoint study records of the publications Zeiger 1992 and Inoue 1980a. However, these studies are not adequate to fulfil this standard information requirement because in Zeiger 1992 the essential fifth strain (*E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102) was not assessed and negative controls were not employed; in Inoue 1980a only two relevant strains were tested. Hence there is not "adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)".
- With respect to REACH requirement Annex VIII, Section 8.4.2., *in vitro* cytogenicity/ micronucleus study, you provided an endpoint study record of the EU RAR 2002. However, the provided data is not adequate to fulfil this standard information requirement because there is not adequate and reliable documentation of the applied test method, i.e. the information provided does not meet the requirements of a robust study summary.[2] In particular, information on the following is missing: Data on GLP compliance; identification of vehicle; data on controls; evaluation criteria; statistics; validity of vehicle controls; validity of negative controls; validity of positive controls; details on results.
- Furthermore, you provided an endpoint study record of the publication Inoue 1980b relating to an *in vitro* mammalian cell transformation test using the source substance CAS RN 7173-51-5 which does not fulfil any of the REACH standard information requirements of Annex VII, Section 8.4.1. or Annex VIII, Sections 8.4.2. and 8.4.3. because the test is not designed to detect clastogens or aneugens (Annex VIII, Section 8.4.2.) nor gene mutations (Annex VII, 8.4.1. and Annex VIII, 8.4.3.). Hence there is not "adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)".
- With respect to REACH requirement Annex VIII, Section 8.6.1., short-term repeated dose toxicity study (28-day), you provided an endpoint study record of a 28-day study in rats with the source substance CAS RN 107-64-2 (ECB 2002).

  According to column 2 of Section 8.6.1., Annex VIII, "*the short-term toxicity study (28 days) does not need to be conducted if: a reliable sub-chronic (90 days) or chronic toxicity study is available, provided that an appropriate species, dosage, solvent and route of administration were used*". In this respect, you provided an endpoint study record of a study equivalent or similar to OECD TG 408 (USA EHA-MT 1970). However, this study is not reliable because the study design does not cover the key parameters of the corresponding test method (OECD TG 408): No data on

[2] See for Article 3(28) of the REACH Regulation and ECHA's "Practical Guide 3: How to report robust study summaries" which is available in the Internet at http://echa.europa.eu/practical-guides

GLP; only 12 animals (6 males and 6 females) used instead of at least 20 animals (10 males and 10 females); no data on ophthalmological examinations, haematology and clinical biochemistry; dose levels only up to 2000 ppm equivalent to approximately 100 mg/kg bw/ day. The endpoint study records of [redacted] (1977) and BIBRA (1987) were not considered for this read-across assessment because the registrant himself disregarded the source substance CAS RN 26062-79-3 and the assignment of reliability 4, respectively. These studies were provided as supporting evidence.

However, even if these studies are considered as supporting evidence for the read-across, read-across prediction is still not possible as there is not "adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)". Therefore, the provided study records for 90-day repeated dose toxicity studies cannot be accepted to adapt the standard information requirement of a short term repeated dose toxicity study (28 days) according to Annex VIII, 8.6.1.

- With respect to REACH requirement Annex VIII, Section 8.7.1., screening for reproductive/developmental toxicity, you provided an endpoint study record of the publication ECB 2002. However, the endpoint study record only contains very limited reporting on the results in particular on findings in offspring (reporting on offspring is limited to increase of percentage of post-implantation losses; viability index on postnatal day 4; body weight). Due to this limited reporting (lack of adequate and reliable documentation), ECHA cannot assess whether all investigations prescribed by OECD TG 421 were performed and with respect to the investigations performed in offspring, you stated that "*it is not reported whether pups had been evaluated for any external abnormalities.*" ECHA therefore concludes that the OECD TG 421 study does not provide "adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)".

  According to column 2 of Section 8.7.1., Annex VIII, "*this study does not need to be conducted if: a pre-natal developmental toxicity study (Annex IX, 8.7.2) ... is available.*" In this respect, you provided endpoint study records of the publications Inoue 1980c (reliability 2) and Palmer 1983 (reliability 4). The source study by Palmer 1983 is inadequate since you have assigned it a Klimisch reliability score of 4. Furthermore, the non-GLP, non-guideline study by Inoue 1980c is not adequate to fulfil the endpoint because it does not cover the key parameters in the corresponding test method (OECD 414); for example: The study uses only 2 dose levels instead of at least three dose levels; administration was only performed on day 7, 9, 11, 13 or 15 of pregnancy instead of daily dosing from implantation to the day prior to scheduled caesarean section; only 7-11 dams per group were used instead of 20 female animals. Therefore there is not "adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)". Hence, the provided endpoint study records for pre-natal developmental toxicity studies cannot be accepted to adapt the standard information requirement of screening for reproductive/developmental toxicity according to Annex VIII, 8.7.1.

Thus for all of the above-listed studies, there is a failure to meet the requirements of Annex

XI, Section 1.5 for "adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)", or for "adequate and reliable documentation".

0.3. Conclusion

The adaptation of the standard information requirements for Annex VII, Section 8.4.1. (*in vitro* gene mutation study in bacteria), Annex VIII, Section 8.4.2. (*in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study), Annex VIII, Section 8.4.3. (*in vitro* gene mutation study in mammalian cells), Annex VIII, Section 8.6.1. (28-day short-term repeated dose toxicity study) and Annex VIII, 8.7.1. (screening for reproductive/ developmental toxicity) is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance by interpolation for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA does not accept the read-across for the above-identified information requirements.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a bacterial reverse mutation assay (OECD TG 471) with the analogue substance CAS RN 68783-78-8 (Zeiger 1992), a bacterial reverse mutation assay (OECD TG 471) with the analogue substance CAS RN 7173-51-5 (Inoue 1980a) and an in vitro mammalian cell transformation test (test method EU B.21) with the analogue substance CAS RN 7173-51-5 (Inoue 1980b).

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Therefore, 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.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

In your comments to the draft decision, you agreed that the test (OECD TG 471) is necessary.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation.

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for an *in vitro* mammalian chromosome aberration test (test method EU B.10) with the analogue substance CAS RN 61789-80-8 (EU RAR 2002) and an *in vitro* mammalian cell transformation test (test method EU B.21) with the source substance CAS RN 7173-51-5 (Inoue 1980b). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Therefore, 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.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments to the draft decision, you agreed that the test (OECD TG 487) is necessary.

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: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an *in vitro* mammalian cell transformation test (test method EU B.21) with the analogue substance CAS RN 7173-51-5 (Inoue 1980b). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Therefore, 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.

ECHA considers that the *in vitro* mammalian cell gene mutation test – *hprt* test (OECD TG 476) and the *in vitro* mammalian cell gene mutation test – Mouse lymphoma assay (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3. In your comments to the draft decision, you agreed that the test (OECD TG 476) is necessary.

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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under points 1 and 2 have negative results.

4. Short-term repeated dose toxicity (28 days), one species, oral route (Annex VIII, Section 8.6.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation.

A "short-term repeated dose toxicity study (28 days)" is a standard information requirement as laid down in Annex VIII, Section 8.6.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a repeated dose 28-day oral toxicity study (OECD TG 407) with the analogue substance CAS RN 107-64-2 (ECB 2002), a repeated dose 90-day oral toxicity study (OECD TG 408) with the analogue substance CAS RN 7173-51-5 (USA EHA-MT 1970), and a repeated dose 90-day oral toxicity study (OECD TG 408) with the source substance CAS RN 61789-77-3 (BIBRA 1987). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the substance is classified as Skin Corr. 1C/ H314 (causes severe skin burns and eye damage) the provided information indicates that human exposure to the registered substance by the inhalation route is not likely because the registered substance is a viscous liquid with a low vapour pressure of 0.0122 Pa at 20°C and a high boiling point of > 158.5 °C (under decomposition). Moreover, no uses which would be of concern for inhalation exposure (e.g. no spraying applications) are identified. Hence, the test shall be performed by the oral route using the test method OECD TG 407.

According to the test method OECD TG 407 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision, you agreed that the test (OECD TG 407) is necessary, and that the test requested in point 5 below (OECD TG 422) will cover the information requested here, under point 4.

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: Repeated dose 28-day oral toxicity study (test method: OECD TG 407) in rats.

5. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.1., "*it is strongly recommended to consider conducting a screening study*" in addition to prenatal developmental toxicity studies, in particular, because the following reproductive toxicity endpoints are not addressed by pre-natal developmental toxicity studies: Mating behaviour, fertility and peri-natal effects whereas they are addressed by the screening study for reproductive/ developmental toxicity (OECD 421 or 422).

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a reproduction / developmental toxicity screening test (OECD TG 421) with the analogue substance CAS RN 107-64-2 (ECB 2002). Furthermore, you have provided two study records for a non-GLP, non-guideline teratogenicity study with the source substance CAS RN 1812-53-9 (Inoue 1980c) and a non-GLP, non-guideline teratogenicity study with the source substance CAS RN 107-64-2 (Palmer 1983). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Therefore, 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.

According to the test methods OECD TG 421 and 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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 viscous liquid with low vapour pressure, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision, you agreed that the test (OECD TG 422) is necessary.

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: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Note for your consideration

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R. 7.6 (version 4.1, October 2015).

6. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation.

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record from a literature study equivalent to ISO 7346. You have considered the study to be reliable with restrictions since it is not performed under GLP and no analytical monitoring was performed. The LC50 in zebrafish is reported to be 0.094 mg/l. While you report the identity of test material to be the same as for the registered substance (CAS 63393-96-4), the name of the test material provided in the endpoint study record is Aliquat 336 (CAS 5137-55-3). Furthermore, the referenced publication (Dave *et al.*, 1981. Toxicity of eight solvent extraction chemicals and of cadmium to water fleas, *Daphnia Magna*, rainbow trout, *Salmo Gairdneri*, and Zebrafish, *Brachydanio Rerio*. *Comparative Biochemistry and Physiology Part C: Comparative Pharmacology* 69 (1): 83-98), does not mention Aliquat 336, but Alamine 336 (CAS 57176-40-6). Hence ECHA cannot assess that the substance tested is the registered substance and its identity cannot be confirmed by the details of the endpoint study record in the technical dossier.

ECHA also notes that, in case the test material is a different substance from the registered substance, you have not claimed an adaptation of the information requirement according to Annex XI, Section 1.5. of the REACH Regulation. Also, as you have provided neither the identity of the source substance and its impurity profile nor any read-across justification, the prediction of the relevant property of the registered substance cannot be made based on the information in the dossier.

Considering the above, ECHA notes that according to REACH requirement Annex VIII, Section 9.1.3, the endpoint requirements are not fulfilled.

You have already classified the substance as Acute Category 1 and Chronic Category 1; therefore, from a safe use perspective the heaviest classification is already in place. However, as the LC_{50} is the one that you used for the PNEC calculation and for the risk assessment, it is important to obtain a correct value for the registered substance and for this endpoint.

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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

In your comments to the draft decision, you agreed that the test (OECD TG 203) is necessary.

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: Fish, acute toxicity test (test method: EU C.1./OECD TG 203).

Appendix 2: Procedural history

ECHA notes that the tonnage band for one member of the joint submission is 10 to 100 tonnes per year.

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 compliance check was initiated on 4 December 2015.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

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.

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. 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.