EUROPEAN CHEMICALS AGENCY

Helsinki, 7 December 2017

Addressee: [redacted]

Decision number: CCH-D-2114376667-32-01/F
Substance name: Betaines, C12-14 (even numbered)-alkyldimethyl
List number: 931-700-2
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28.05.2015
Registered tonnage band: 1000+T

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. **Skin corrosion/irritation (Annexes VII and VIII, Section 8.1.) with the registered substance:**
   i. Skin corrosion, *in vitro* (Annex VII, Section 8.1., test method: EU B.40/OECD TG 430, or EU B.40bis/OECD TG 431 or OECD TG 435); and
   ii. Skin corrosion/irritation, *in vivo* (Annex VIII, Section 8.1., test method EU B.4/OECD TG 404) only in case the *in vitro* skin corrosion test method(s) are not applicable for the substance, or the results from the study(ies) are not adequate for classification and risk assessment.

2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance ;**

3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

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

5. **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;**

6. **Identification of DNEL(s) and risk characterisation (Annex I, Section 1.4. and 6.): revise and derive acute and long-term DNEL(s) for workers and for**

the general population inhalation and dermal route for systemic and local effects using the assessment factors according to ECHA Guidance R.8 for DNEL derivation using the study giving rise to the highest concern and revise the risk characterisation accordingly *or* provide a detailed justification for not using the recommendations of ECHA Guidance R.8 for DNEL derivation and the study giving rise to the highest concern. The results of the studies requested with this decision must be taken into account when revising the DNELs.

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 to the REACH Regulation. 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 adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by ***14 June 2022*** except for the information requested under point 1 for skin irritation or skin corrosion testing and under point 2 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **14 June 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 5 after **16 September 2019**, unless an indication to the contrary is communicated to you by ECHA before that date. 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 and 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, has to 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.

EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

You have sought to adapt the information requirements for:

- *Skin corrosion/irritation (Annexes VII and VIII, Section 8.1.);*
- *Sub-chronic toxicity (90-day) study (Annex IX, 8.6.2.);*
- *Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species*
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.); and

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

You have additionally sought to adapt the information requirements for "*Skin corrosion/irritation (Annexes VII and VIII, Section 8.1.)*" by applying an endpoint-specific read-across adaptation. This endpoint-specific read-across adaptation is addressed under section 1.

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".

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 an property-specific context.

Description of the grouping and read-across approach proposed by the Registrant

You consider that compliance with the REACH information requirements for the registered substance Betaines, C12-14 (even numbered)-alkyldimethyl (hereafter referred to as the 'target substance') can be achieved by using data from the following structurally similar substances: Betaines, C12-14 (even numbered)-alkylmethyl, CAS No 68424-94-2 (EC No 270-329-4; hereafter the 'source substance 1'); Dodecyl dimethyl betaine, CAS No 683-10-3 (EC No 211-669-5; hereafter the 'source substance 2'); Tetradecyldimethyl betaine, CAS No 2601-33-4 (EC No 220-006-9; hereafter the 'source substance 3'); 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-,N-(C8-18 (even numbered), C18 unsaturated acyl) derivs., hydroxides, inner salts, CAS No 61789-40-0 (EC No 263-058-8; hereafter the 'source substance 4'); 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-(C8-18 acyl) derivs.,hydroxides, inner salts (hydrogenated), CAS No 97862-59-4 (EC No 308-107-7; hereafter the 'source substance 5'); and Alkyl (C12-C16) dimethyl ammonio acetate, CAS No not provided (EC No not provided; hereafter the 'source substance 6').

You have provided read-across documentation as an attachment in IUCLID, Section 13, where you are using an analogue approach to predict the toxicological properties of the target substance based on the available data from the source substances (see above).

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group:

(a) Source and target substances are structurally similar: *"Target and all source chemicals share the properties of amphoteric surfactants, being structurally closely related.*

(b) Source and target substance have similar physico-chemical properties: *"Similar physico-chemical properties support the analogue approach between the target substance and identified source substances".*

(c) Common properties for environmental fate & eco-toxicological profile: *"The substances are readily biodegradable, have no significant potential for bioaccumulation and have a low adsorption potential. Furthermore, the available data indicate the same ecotoxicologigal profile; all available data are in the same order of magnitude"*

(d) Toxicokinetics: *"Based on the chemical structure of Betaines, C12-14 (even numbered)-alkyldimethyl, metabolism into chemically reactive compounds under in vivo conditions is unlikely".*

(e) Similar (low) toxicity profiles: You have submitted QSAR predictions and study records to support this argument.

You propose that the source and registered substances have similar (low) toxicity profiles for the above-mentioned information requirements. ECHA understands this as the hypothesis under which you make predictions for the properties listed above.

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

With regard to the justification for read-across, ECHA has the following observations:

(a) Explanation on why and how the structural similarities allow predictions

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, it has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation.

ECHA notes the target and source substances are UVCB substances that share a common structural feature, *i.e.* all substances are 'betaines'. However, ECHA notes the target substance and the proposed source substances also display significant stuctural differences which are caused by the variations in the carbon chain lengths of the 'alkyl'-fragment. Moreover, source substances 4 and 5 are alkyl amidopropyl betaines, whereas the target substance and source substances 1-3 and 6 are alkyl dimethyl betaines.

ECHA concludes that you have not addressed the structural/compositional differences between the source substances and the target substance and did not sufficiently explain why those differences would not lead to differences in the toxicity profile of target and source substances. Therefore, your hypothesis cannot be considered as valid to establish a scientific credible link between the structural similarity and the prediction.

(b) Similar physico-chemical properties

Your proposed adaptation argument is that the physico-chemical similarity between the source and target substances is a basis for predicting the properties of the target substance. This argument is limited and is in principle not capable of being sufficient. A likelihood of physico-chemical similarity as a result of structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that physico-chemical similarity per se is sufficient to enable the prediction of human health properties of a substance. This is because physico-chemical similarity does not always lead to predictable or similar human health properties. Further elements are needed[2], 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. You have not provided such elements in your dossier.

ECHA notes that in your read across justification document you also indicate that "*very limited experimental information on analogue substances* (about their physicochemical properties) *is available*" and you provide expert statements for the vast majority of the physicochemical properties. As a result of the lack of data for the source substances, ECHA cannot compare the physicochemical properties of source and target substances and establish whether indeed they are similar or follow a regular pattern. Therefore, ECHA considers that your argument about similar physico-chemical properties between the target and the source substances is not supported.

(c) Common properties for environmental fate & eco-toxicological profile

Your proposed adaptation argument is that the ecotoxicological similarity between the source and target substance is a basis for predicting the properties of the substance. This argument is limited and is in principle not capable of being sufficient. A likelihood of ecotoxicological similarity as a result of structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept that ecotoxicological similarity per se is sufficient to enable the prediction of human health properties of a substance. This is because ecotoxicological similarity does not always lead to predictable or similar human health properties. Further elements are needed[3], 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. You have not provided such elements in your dossier.

(d) Toxicokinetics

You have provided theoretical considerations on the ADME properties for the target substance based on physical-chemical properties and the available data from source substances. You conclude that absorption is likely via the oral and dermal routes and that the target substance is unlikely to be metabolised to reactive metabolites and its largest part is excreted predominantly in the feaces; this is based on a study on cocamidopropyl betaines (CAPB) not present in the technical dossier (HERA 2005, http://www.heraproject.com/files/45-hh-e101023f-d12f-6a30-deb0770e9bf8e4d0.pdf).

ECHA notes that there is no toxicokinetic information available for the target substance, therefore it is not possible to verify the assumptions. You claim that the substances are assumed to have similar toxicokinetic properties, but the assumption of similarity is not an adequate basis to demonstrate that there are similar toxicokinetic parameters (i.e. ADME

[3] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals and ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

properties). On this basis, your argument of similar toxicokinetic properties is not a reliable basis to predict the properties of the registered substance.

Additionally, ECHA considers that you have not explained how the repeated dose toxicity profiles of the source substances 1 and 6 (presented in point (e) below) can be explained by the assumed similarities in toxicokinetic properties. Two different substances may have similar toxicokinetic properties, but the structural dissimilarity may cause different toxicodynamic properties, and hence markedly different toxicity between the two substances. In the absence of such information on the toxicodynamic properties of the registered substance, there is not an adequate basis for predicting the properties of the registered substance from considerations based on the toxicokinetic properties of the source and registered substances.

(e) Similar (low) toxicity profiles

Your proposed adaptation argument is that the toxicological similarity between the source and target substances is a basis for predicting the properties of the substance. This argument is limited and is in principle not capable of being sufficient. A likelihood of toxicological similarity as a result of structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that toxicological similarity per se is sufficient to enable the prediction of human health properties of a substance. This is because toxicological similarity in one or multiple endpoints does not always lead to predictable or similar human health properties in other endpoints. Further elements are needed[3], 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. You have not provided such elements in your dossier.

You argue that the OECD QSAR toolbox supports the read-across approach by providing a similar toxicological profile for the source and target substances. However, the methodology used to provide these profiles is not stated, and consequently ECHA is unable to evaluate what this information is. Therefore, the results cannot be used to verify a prediction made for the properties under consideration. Furthermore, as explained in the next paragraph, the source substances also appear to differ with regard to repeated dose toxicity, which is in apparent contrast to the results of the profiling tool.

Further, your hypothesis is that the source and registered substances have similar (low) toxicity profiles, and as a minimum, one would expect that these substances would affect the same biological targets. ECHA notes that there is no repeated dose toxicity information available for the target substance which would allow a side-by-side comparison of the toxicity profiles with the source substances. Repeated dose toxicity information is available only for source substances 1 and 6:

- In the OECD 408 study with source substance 1, you report that local irritative effects related to gavage dosing were observed in the forestomachs demonstrated by papillomatous hyperplasia of the mucosa, high-grade inflammation and ulcer formation in the high dose group (500 mg/kg/day); and as irritative changes in the forestomach ranging from slight to moderate up to ulcer formation in the mid dose group (250 mg/kg/day). You state that there are no other treatment related effects in the study. You set a NOAEL at 250 mg/kg/day for systemic toxicity (based on the observed local effects).
- In the OECD 422 study with source substance 6, stomach effects were observed including ulceration, squamous hyperplasia, submucosal inflammation and oedema. You set the NOAEL at 50 mg/kg/day (lowest dose tested) based on effects in kidney and urinary bladder that were considered sequential to irritant effects of the test

substance or its metabolite(s) excreted in urine. In the kidneys, urothelial and collecting duct hyperplasia occurred (in high dose group) and urothelial hyperplasia in the urinary bladder was observed (in one male of the high dose group and in females of the mid and high dose groups). In addition, test item-related changes in the adrenal glands and bone marrow were observed in the study.

The sub-chronic toxicity study conducted with source substance 1 has longer treatment duration, higher doses tested, higher betaine content of the tested substance and higher statistical power compared to the sub-acute toxicity study conducted with source substance 6. However, the study with source substance 6 showed different biological effects (i.e. on kidney, bladder, adrenal glands and bone marrow) which were not observed with source substance 1. This demonstrates that the toxicity profiles of the substances differ. Your hypothesis that there is similar toxicity cannot be supported by the experimental data, and consequently, there is not a reliable basis for the prediction of the properties of the registered substance.

(f) Bias in the selection of source substances and/or source studies

ECHA notes that you have not clearly explained how you have selected the source substances for your prediction and also why other similar substances are not being considered. ECHA indicates that there are additional analogues described in the OECD SIAM 23 (Oct 2006, http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=f588b2b9-9862-45e3-804b-1e3113bc85ec) for the chemical category 'Alkylamidopropyl betaines'. Specifically, there are additional repeated dose toxicity studies and pre-natal developmental studies available with this category.

Furthermore, ECHA notes that the US EPA has grouped the substances in a different grouping approach, where the 'alkyl amidopropyl betaines' form a distinct subcategory of "aclyl amino propanaminium amphoterics" in US EPA "Fatty nitrogen-derived amphoterics category" (June 2010; http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.175.5435&rep=rep1&type=pdf). EPA also creates a separate subcategory for the "alkyl aminium amphoterics" (synonym of 'alkyl dimethyl betaines') in the same document and expects the latter to be more hydrophobic than the first subcategory because they do not contain the amide group.

Moreover, HERA 2005 (http://www.heraproject.com/files/45-hh-e101023f-d12f-6a30-deb0770e9bf8e4d0.pdf) identifies additional potential analogues.

Finally, ECHA notes the potential analogue substance 1-Hexadecanaminium, N-(carboxymethyl)-N,N-dimethyl-, inner salt, CAS No 693-33-4), which is an alkyl dimethyl betaine as the target substance. There are additional pre-natal developmental toxicity studies available conducted with this compound (https://ofmpub.epa.gov/oppthpv/quicksearch.display?pChem=101164):

- Arnold, K. S., J. L. Schardein and M. Blair. Oral Teratology Study of 1-Hexadecanaminium in Rats. 1985. International Research and Development Corporation, U. S.
- Hoberman, A. M. and M. S. Christian. 1984. Initial submission: Pilot Study for Percutaneous Teratology of 1-Hexadecanaminium & 5% Isopropanol in Rabbits with Attachments and Cover Letter Dated 07/279/2. EPA document number 88-920004922. [redacted]
  The US-EPA's evaluation of the study by Arnold *et al* concludes: "*In a prenatal developmental toxicity study in rats administered CASRN 693-33-4 via gavage, decreased body weight gain was observed at 50 mg/kg-day (the lowest dose tested) and above; a NOAEL for maternal toxicity was not established. Reduced or absent*

ossification of the skull was observed at 250 mg/kg-day; the NOAEL for developmental toxicity is 150 mg/kg-day". This study gives rise to a higher concern with regard developmental toxicity compared to the submitted PNDT study in the registration dossier conducted with source substance 5 [CEFIC/CESIO[ICCA Initiative] Alkylamidopropyl Betaines Consortium (2004)].

In summary, there are a variety of structurally-related substances and some of these have disparate toxicological properties. You have not clearly explained your basis for choice of source substances (and disregarding other potential source substances), and so ECHA concludes that it is not possible to verify that you have selected the source substances that are most appropriate for your read across approach. On this basis, ECHA considers that your proposed read-across cannot be considered a reliable basis for prediction of the properties of the registered substance.

(g) Substance characterisation of source substances

The substance characterisation of the source substances need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4), it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* 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 notes that in Table 2 in the read-across justification document, you provide compositional information for the source substances. However, this information is incomplete since you do not specify the concentration of the different constituents but you only provide either distribution ranges or higher concentrations; therefore ECHA can not compare compositions between the source and target substances. In addition, purity/impurity information has not been provided for the test substances under endpoint study records. Further, you have not addressed the impact of impurities on the toxicity profiles of the target and source substances.

Hence, these data cannot be assessed using the information provided in the registration dossier and the suitability of the source substances for predictions based on read-across purposes cannot be verified.

In the comments you submitted you propose a two-stage approach to update the dossier in order to prevent any unnecessary animal testing: first, a full investigation will be conducted to gather all existing data and to develop your grouping and read across justification and then, if needed, the conduct of studies will follow.

There is still a possibility of providing an adaptation to the information requirements for your registration dossier. As stated above, the present decision states "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."

Failure to comply with the request in the decision, or to otherwise fulfil the information requirement with a valid and documented adaptation, shall result in a notification to the Authorities of the Member States for possible enforcement.

With regard to the possible future generation of an adaptation, ECHA cannot evaluate this approach now as it does not exist yet. ECHA will initiate the follow-up evaluation of the updated registration dossier when the deadline in the decision has passed. Then it will establish whether the information submitted in an updated dossier meets the respective information requirements of REACH.

Please note our factsheet describing the follow-up process to dossier evaluation decisions at: http://echa.europa.eu/view-article/-/journal_content/title/new-factsheet-explaining-the-follow-up-to-dossier-evaluation-decisions.

Further, in your comments on the draft decision, you provided a proposed course of action to address ECHA's read-across assessment, which will culminate in the preparation of a new read-across justification report.

In addition, you listed "[redacted]" (Appendices 1 and 2 in "[redacted]" document).

ECHA notes that you did not submit any revised read-across justification or adaptation according to the criteria established in Annex XI of the REACH Regulation. Moreover, the additional source substances' data you provided on the skin corrosion/irritation, sub-chronic and pre-natal developmental toxicity properties include only references of assessment documents from other evaluating agencies and at best NOAEL / LOAEL values and therefore ECHA cannot evaluate them. Consequently, the additions above do not change the conclusion below.

Conclusion on the read-across approach

The adaptation of the standard information requirements for the endpoints: Skin corrosion/irritation (Annexes VII and VIII, Section 8.1.); Sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.); Pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.); and Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) in the technical dossier 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 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 rejects all adaptations in the technical dossier that are based on Annex XI, Section 1.5.

1. Skin corrosion/irritation (Annexes VII and VIII, Section 8.1.)

"Skin corrosion/irritation" is a standard information requirement as laid down in Annex VII, Section 8.1. of the REACH Regulation: The assessment of this endpoint shall comprise the following steps: Skin corrosion, *in vitro* (Annex VII, Section 8.1.1.) and Skin irritation, *in vitro* (Annex VII, Section 8.1.2.). As laid down in Annex VIII, Section 8.1., an *in vivo* study for skin corrosion/irritation shall be considered only if the *in vitro* studies under points 8.1.1 and 8.1.2 in Annex VII are not applicable for the substance, or the results of these studies are not adequate for classification and risk assessment. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

However you have not provided a complete assessment of skin corrosion/irritation in the dossier that would meet the information requirement of Annex VII, Section 8.1 and Annex

VIII, Section 8.1.

Specifically, you have provided the following studies for which you report that they were conducted with the registered substance, although the test substances in these studies were different than the registered substance, as ECHA indicates below:

A. Key study; 31% aqueous formulation of test substance (30% conc. of active is reported); Reliability 1; 1994; GLP; according to OECD 404;
test substance composition: C12 (65-75%), C14 (22-28%), C10 (max. 4%)
[registered substance composition as stated in section 1.2 of your IUCLID dossier C12: [redacted]%, C14: [redacted]%, C10: not present];
New Zealand White rabbit; according to CLP criteria classification as Skin Irritant Cat.2 is warranted.

B. Supporting study: aqueous formulation of test substance; Reliability 2; 1987; similar to OECD 404; New Zealand rabbit; composition of the test substance and concentration in water not provided; test material is "Empigen BB" which is commercial name of Betaines, C12-14-alkyldimethyl (Lauryl betaine) CAS No 66455-29-6; according to CLP criteria no classification is warranted.

C. Supporting study: aqueous formulation of test substance; Reliability 2 (reported deviations: no reading in 48 hrs, test terminated after 72 h, no information regarding reversibility, purity of test substance not reported, 24h occlusive dressing); 1978; similar to OECD 404; New Zealand rabbit; test material is "Empigen BB" which is commercial name of Betaines, C12-14-alkyldimethyl (= Lauryl betaine) CAS No 66455-29-6; according to CLP criteria no classification is warranted, although in RSS is stated "Empigen BB has well-defined irritating effects to rabbit skin". It not clear from where this conclusion is drawn.

ECHA observes that the submitted tests were conducted with aqueous formulations of other substances and not with the registered substance subject to the present decision. Thereby ECHA understands that you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation governing grouping of substances and read-across approach. However, you have not provided any justification for the use of other substances, nor any other basis for predicting the properties of the registered substance from these source substances. There is therefore a failure to meet the requirement of Annex XI, 1.5 to provide adequate and reliable documentation, and your adaptation is therefore rejected.

Additionally, according to OECD TG 404 "*When testing solids ..., the test chemical should be moistened with the smallest amount of water*". ECHA observes that the three studies were conducted aqueous formulations instead of the pure substances.Therefore, the tests are not guideline compliant and they do not provide adequate information for classification and risk assessment. Thus, the information you submitted does not meet the information requirement of Annexes VII and VIII, Section 8.1.

Additionally, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records of 2 studies (OECD TG 404) with source substances 1 and 2 (CAS No 68424-94-2 and 683-10-3, respectively)]. ECHA notes that in both studies, no information regarding the composition of the tested material is provided. ECHA considers that detailed information of the composition of the test material used is required to establish the relation to the target substance; and consequently a pre-requisite to any predictions. In the absence of this information, it cannot be verified that source substances 1 and 2 can be used to predict properties of the target substance.

Moreover, both studies were conducted with aqueous formulations instead of the pure substances. ECHA highlights that according to the OECD TG 404 "*When testing solids ..., the test chemical should be moistened with the smallest amount of water*". Therefore, ECHA concludes that the tests you provided are not in accordance with OECD TG 404 and thus they cannot be used to fulfil the standard information requirements.

Further, as explained in "ECHA's analysis of the grouping and read-across approach" paragraph in this Appendix, your adaptation of the information requirement by use of read-across is rejected by analogy.

In the comments on the Draft Decision, you submitted a stepwise approach in order to address the request for skin corrosion/irritation study. With regard to the stepwise approach see ECHA's response at the end of "Grouping of substances and read-across approach" section.

You also identified additional potential source substances and data on skin corrosion/irritation in Appendices 1 and 2 in "[redacted]" document. However, this information does not change the conclusion on read across as explained at the end of "Grouping of substances and read across approach" section. Additionally, the identified data include only references of assessment documents from other evaluating agencies; therefore, ECHA cannot to evaluate them. Hence, these data do not meet the information requirement.

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. As the information provided in the dossier by using aqueous formulations containing the registered substance give a clear indication that the registered substance is either corrosive or irritant to the skin, ECHA considers that more information is needed in order to make an adequate conclusion for classification and risk assessment.

The potential (non-)corrosive properties of the substance can be assessed by performing an *in vitro* skin corrosion study with the registered substance to either confirm or exclude skin corrosive properties.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information on skin corrosion/irritation derived with the registered substance subject to the present decision:

a. *in vitro* study for skin corrosion (test method: EU B.40./OECD TG 430 or B.40 bis./OECD TG 431 or OECD TG 435), *and*
b. *in vivo* study for skin corrosion/irritation (test method: (EU B.4/OECD TG 404) only in case the *in vitro* skin corrosion test method(s) are not applicable for the substance, or the results from the study(ies) are not adequate for classification and risk assessment.

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.

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. 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 sub-chronic toxicity study (OECD

TG 408) conducted with source substance 1 and a screening toxicity study OECD 422 conducted with the source substance 6.

However, as explained above in "ECHA's analysis of the grouping and read-across approach" paragraph in this Appendix, your adaptation of the information requirement is rejected. Additionally, the OECD 422 study on source substance 6 does not cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3), and thus this source study fails to meet the requirement of Annex XI, 1.5.

In the comments to the Draft Decision, you submitted a stepwise approach in order to address the request for subchronic toxicity study. With regard to the stepwise approach, see ECHA's response at the end of "Grouping of substances and read-across approach" section above.
You also identified additional potential source substances and data on subchronic toxicity in Appendices 1 and 2 in your "[redacted]" document. However, this information does not change ECHA's conclusion on read across as explained at the end of "Grouping of substances and read across approach" section above. Additionally, the identified data include only references of assessment documents from other evaluating agencies and at best NOAEL/LOAEL values; therefore, ECHA cannot to evaluate them. Hence, these data do not meet the information requirement.

In your comments, you also indicate that you may submit a testing proposal to address to information requirement set by ECHA. Since this information requirement is already subject to this compliance check process, it follows that ECHA would consider a possible future testing proposal to be inadmissible while the compliance check for this information requirement is already ongoing.

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 has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and 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 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

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.

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 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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 for the first species sought to adapt the information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Prenatal developmental toxicity study in rats (OECD TG 414) with source substance 5.

However, ECHA notes that the test material is only identifed by the chemical name and CAS No; no other information on its composition is provided. ECHA considers that detailed information on the composition of the test material used is required to establish the structural similarity with the target substance; and consequently is a pre-requisite for any predictions. In the absence of this information, it cannot be verified that source substance 5 can be used to predict properties of the target substance.

Moreover, as explained in "ECHA's analysis of the grouping and read-across approach" in this Appendix, your adaptation of the information requirement is rejected.
In the comments on the Draft Decision, you submitted a stepwise approach in order to address the request for prenatal developmental toxicity study in first species. With regard to the stepwise approach, see ECHA's response at the end of "Grouping of substances and read-across approach" section.

You also submitted additional potential source substances and data on prenatal developmental toxicity in Appendices 1 and 2 in [redacted] document. However, this information does not change the conclusion on read across as explained at the end of "Grouping of substances and read across approach" section. Additionally, the identified data include only references of assessment documents from other evaluating agencies and at best NOAEL/LOAEL values; therefore, ECHA cannot to evaluate them. Hence, these data do not meet the information requirement.

Further, you indicated that you may submit a testing proposal for the PNDT study in the 1st species. With regard to the inadmissibility of the testing proposal, see ECHA response under section 2 above.

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 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 assumption ECHA considers testing should be performed with rats or rabbits as a first 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 6.0, July 2017) 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 first species (rat or rabbit) by the oral route.

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

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).

You have for the first species sought to adapt the information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Prenatal developmental toxicity study in rats (OECD TG 414) with source substance 5. However, as explained in point 3 and in the Appendix, your adaptation of the information requirement is rejected.

There is no information provided for a pre-natal developmental toxicity study in a second species; and the technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

With regard to your comments on the Draft Decision about the stepwise approach and the additional potential source substances and data on prenatal developmental toxicity, see ECHA's response at the end of "Grouping of substances and read-across approach" section and at section 3.

Further, you indicated that you may submit a testing proposal for the PNDT study in 2st species. With regard to the inadmissibility of the testing proposal, see ECHA response under section 2 above.

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 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 rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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 6.0, July 2017) 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 (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

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

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. Further detailed guidance on study design and triggers is provided in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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 provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement according to Annex IX, Section 8.7., column 1. of the REACH Regulation. You provided the following justification for the adaptation *"According to Regulation (EC) No 1907/2006, Annex IX, 8.7.3. column 1, a 2-generation study for assessment of reproductive toxicity is not required as no adverse effects on reproductive organs were reported in the subchronic 90-day study".*

ECHA notes that you have registered the substance at Annex X level and therefore the Annex IX adaptation is not relevant or applicable to your registration.

Further, you have sought to adapt the information requirement according to Annex XI, Section 1.5. of the REACH Regulation governing grouping of substances and read-across approach by providing study records for:

- a sub chronic 90-day toxicity study with source substance 1.
- a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with source substance 6.

ECHA has evaluated the information and documentation provided in the registration dossier in light of the requirements of Annex XI, Section 1.5 of the REACH Regulation and concludes that the requirements of Annex XI, Section 1.5 are not met for the reasons listed in "ECHA's analysis of the grouping and read-across approach" in this Appendix. Additional reasons specific for the documentation you provided on reproductive toxicity are explained below:

ECHA notes that the provided subchronic 90-day study as well as the provided "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" do not provide the information required by Annex X, Section 8.7.3. because they lack information on major relevant elements of the requested extended one-generation reproductive toxicity study required at this tonnage level: They provide only limited information on the effects on functional fertility, histopathology of the reproductive organs and postnatal development (including sexual development). Thus, they do not allow a conclusion/decision on the lack of effects on the reproductive toxicity for hazard class sexual function and fertility.

In addition, they do not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.

With regard to your comments on the Draft Decision about the stepwise approach, see ECHA's response at the end of "Grouping of substances and read-across approach" section above.

Further, you indicated that you may submit a testing proposal for the EOGRTS. With regard to the inadmissibility of the testing proposal, see ECHA response under section 2 above.

Hence, 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

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017). The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

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 6.0, July 2017).

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.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) 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 6.0, July 2017) 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.

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 2) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by ***14 June 2019*** *from the date of the decision*. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **16 September 2019** (i.e. within three months after expiry of the 18-month deadline to provide the sub-chronic toxicity study (90-day) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by ***16 September 2019***, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision ***14 June 2022***.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design

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.

6. Identification of DNEL(s) and risk characterisation (Annex I, Sections 1.4. and 6.)

Annex I, Section 1.1.4. of the REACH Regulation requires that the study or studies giving rise to the highest concern shall normally be used to draw a conclusion. It also requires that a robust study summary shall be prepared for that study or studies and included in the technical dossier. In addition, Annex I, Section 1.1.4. requires that if a study giving rise to the highest concern is not used, then this shall be fully justified.

Annex I, Section 1.4.1. of the REACH Regulation requires the Registrant to establish DNEL(s) "*reflecting the likely route(s), duration and frequency of exposure.*" It is also required that "*taking into account the available information and the exposure scenario(s) in Section 9 of the Chemical Safety Report it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans liable to exposure indirectly via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure.*"

Further, Annex I, Section 1.4.1 of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:

a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
b) the nature and severity of the effect;
c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
d) and that the DNELs reflect the likely route(s), duration and frequency of exposure.

The ECHA Guidance on information requirements and chemical safety assessment chapter R.8 provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information to fulfil the REACH obligations.

ECHA identified that the following aspects in your DNEL derivation are not in accordance with the recommendations provided in the ECHA Guidance R.8:

Incorrect selection of starting point
As already explained in the section "ECHA's analysis of the grouping and read-across approach" above in this Appendix, your read-across adaptation is rejected and consequently, the proposed study conducted with the source substance 1 cannot be used for the DNEL derivation.

However, ECHA makes the following observations as far as your selection of starting point is concerned:

You have used the 90-day oral RDT study conducted with the source substance 1 as your starting point in DNEL derivation. The only adverse effect observed in the study was irritation in forestomach. You report NOAEL for the active ingredient 145 mg/kg bw.

In the screening study OECD 422 conducted with the 6th source substance, you have set the $NOAEL_{systemic}$ at 50mg/kg bw (low dose) based on histopathologic changes in kidney (minimal granular casts) and urinary bladder (urothelial hyperplasia). The NOAEL of 50 mg/kg/bw is considerably lower than the NOAEL of 145 mg/kg/bw in the 90 day oral study

with source 1. ECHA notes that for the accurate comparison of the NOAEL values the betaine content of the test substances should be taken into account. You have not provided the appropriate information on the test material of either study in order to make comparison of the NOAEL values. Nevertheless, you have reported in your CSR document in point 5.11.1 (p. 170), that in the 90-day study the betaine content of the test compound is higher than in the screening study, which indicates the much higher toxicity of the test material in the latter study. In addition, the adverse effects in the screening study are considered much more severe than in 90 day study.

Therefore, even if a read-across would be plausible, you should have used the NOAEL of 50 mg/kg/bw corrected for betaine content as your starting point and apply the Assessment Factor of 6 for extrapolation from sub-acute to chronic effects, since the exposure duration of the screening study was minimum 4 weeks for males and approximately 7 weeks for females.

Incorrect modification of starting point

You have submitted no substance-specific data on the absorption for the oral and inhalation route of exposure.

As indicated in ECHA's Guidance R.8 paragraph R.8.4.2: in the absence of route-specific information on the starting route, a default factor of 2 is proposed to be included in the case of oral-to-inhalation extrapolation. You refer to arguments raised in a document "Scientific arguments of relevance for the delineation of a DNEL" without providing this document or any reference to it. Therefore, ECHA is not in a position to assess the scientific validity of those arguments.

For the dermal absorption value, you have submitted an *in vitro* dermal penetration study in mouse conducted with source substance 2 (CAS No 683-10-3) for which you provide no information about the concentration of the different constituents in the test material. ECHA considers that detailed information of the composition of the test material is fundamental to establish its relation to the registered substance. In the absence of this information, it cannot be verified that source substance 2 can be used to predict the dermal absorption of the registered substance.

Moreover, ECHA observes that although you consider 10% dermal absorption in your risk characterisation calculation based on the results of this study, you also report in your read-across justification document that the results of the study indicated a high dermal absorption potential. Specifically, you report that at 24 hrs time point, 25% of the substance was detected in the skin and the measured dermal penetration was 46.5%. In addition, significant impairment of the skin barrier was observed.

In the same document you indicate that since the registered substance "*is considered as corrosive in humans, an enhanced penetration of the substance due to local skin damage cannot be excluded ... QSAR prediction for the skin absorption potential of Betaines, C12-14 (even numbered)-alkyldimethyl resulted in a medium high dermal absorption potential of about 40%*".

Taking into account the afore-mentioned information, ECHA concludes that the dermal absorption of the test substance is well above 10% and that the dermal absorption of the registered substance should be considered at least equal to its oral absorption as indicated in ECHA's Guidance R.8.4.2, although for corrosive substances an even higher dermal absorption value up to 100% could also be argued.

Non-justified use of non-default Assessment Factors (AF):

In your risk assessment, AF of 2.5 for the remaining interspecies variability is missing, whereas you have applied AF for intraspecies variability 3 for workers and 5 for public, instead of 5 and 10 respectively, recommended in ECHA Guidance R.8.

ECHA notes that the reference to the ECETOC guidance AFs cannot replace the ECHA Guidance which has been agreed between all stakeholders, including industry representatives.

With regard to this issue you are given two options:

1. To revise the DNELs for workers and for the general population by applying the assessment factors recommended by ECHA that are appropriate in this case as specified above and, subsequently, re-assess related risks, or
2. In the alternative, you shall, in accordance with Annex I, Section 1.4.1, provide a full justification for the DNELs derived for workers and for the general population provided in the chemical safety report by specifying how the following has been taken into account:
    a. the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
    b. the nature and severity of the effect;
    c. the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
    d. and that the DNELs reflect the likely route(s), duration and frequency of exposure.

Missing DNEL values

ECHA notes that you have not derived a reference value for:

- acute and long-term inhalation, local effects and acute and long-term dermal, local effects to demonstrate that in spray application the risk for respiratory tract and skin exposure is controlled. Local effects in forestomach were observed in the screening study OECD 422 conducted with the source substance 6 from the lower dose tested and therefore you should have set a LOAEL for local effects at this dose and you should have derived DMELs for local dermal and inhalation effects and consider them in your risk characterisation.
- acute dermal systemic effects.

You have justified the omission of those reference values with the following arguments:

- *"Inhalation Local effects - Long-term, acute: Due to the most frequently marketed forms of the substance as aqueous solutions and a low vapour pressure, exposure via the inhalative route is unlikely. If handled in powder form it is common to use personal protective equipment like dust masks to avoid inhalation due to the known irritating potential of the substance".*
- *"Dermal Local effects - Long-term: Due to the known irritating potential of the most frequently marketed forms of the substance as aqueous solutions it is common to use personal protective equipment like gloves to avoid dermal contact; therefore, considering local DNELs for dermal exposure can be omitted".*
- *"Dermal Systemic effects - Acute: Use of personal protective equipment like gloves in order to avoid dermal contact due to the known irritating potential of the substance is established; in addition, data for structurally closely related substances demonstrate a lack of toxicity via the dermal route and a negligible dermal absorption. Therefore, derivation of a short-term systemic DNEL for dermal exposure can be omitted".*

ECHA considers those arguments not valid as:

- The use of Personal / Respiratory Protection Equipment (PPE/RPE) by professionals and consumers reduces exposure levels but it does not exclude exposure.

- The registered substance has a high dermal penetration potential as presented above in the paragraph "*Incorrect modification of starting point*".
- Strong corrosion/irritation effects have been observed in the forestomach which is considered, due to its low pH, less sensitive to local irritation than the respiratory tract and skin.
- The available data indicate that the substance is irritating to the eyes/skin in spray formulations and thus there is potential for irritation.

Therefore, a risk characterisation is needed for acute dermal, systemic effects; long-term inhalation, local effects and long term dermal, local effects either quantitatively based on DMELs or qualitatively according to ECHA's Practical Guide on "How to undertake a qualitative human health assessment and document it in a chemical safety report".

In the comments submitted on the Draft Decision, you proposed the following steps for the derivation of DNEL(s) values: 1. Assessment of all data to identify the study or studies of highest concern. 2. Revision of existing and derivation of new DNELs, documented in a detailed and transparent manner, using the appropriate ECHA default AFs and/or substance-specific data. 3. Revision and/or redrafting of the RC section of the CSR. Based on this, ECHA understands that you agree with ECHA's request.

As explained above, the information provided on DNEL for the registered substance in the chemical safety report does not meet the general provisions for preparing a chemical safety report as described in Annex I, 1.4.1.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to revise and derive acute and long-term DNEL(s) for workers and for the general population for inhalation and dermal route and for systemic and local effects using the study giving rise to the highest concern and the default assessment factors and other recommendations of ECHA Guidance R.8 for DNEL derivation and revise the risk characterisation accordingly *or* provide a detailed justification for not using the recommendations of ECHA Guidance R.8 for DNEL derivation. The results of the studies requested with this decision must be taken into account when revising the DNELs.

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 12 months for requests 1 and 2 and 48 months for the remaining requests, from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the two deadlines, from 12 to 24 months and 48 to 60 months. You sought to justify this request by considering the limited current capacity of many EU testing laboratories without substantiating evidence. Hence, ECHA requested that you submit documentary evidence supporting the requested extension. Following this request, you submitted the tentative timing schedule from the laboratory on the planned timeline for the sub-chronic toxicity (90-day) study and the extended one-generation reproductive toxicity study, intended to start after mid-December 2017. ECHA notes that the planned timeline does not exceed the standard time indicated to you however, considering the predicted timeline for the processing of this decision ECHA understands that you may need a deadline extension. Therefore, ECHA has only partially granted the request and set the deadline for requests 1 and 2 to 18 months and the deadline for the remaining requests to 54 months.

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 compliance check was initiated on 17 November 2016.

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 took into account your comments and did not amend the request(s).
Note that references to the REACH Annexes of request 1 (Skin corrosion/irritation; reference of "Skin corrosion, in vitro") and of request 5 (Extended one-generation reproductive toxicity study) on p. 1 were corrected for clarity.

ECHA took into account your comments and amended the deadline.

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

ECHA received proposal(s) for amendment and did not modify the draft decision.

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

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 in its MSC-56 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 the start of substance evaluation in 2019.

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 requests in this decision, or to otherwise fulfil the information requirements 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 tests 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 tests 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 tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.