EUROPEAN CHEMICALS AGENCY

Helsinki, 3 April 2019

Addressee: [redacted]

Decision number: CCH-D-2114462281-55-01/F
Substance name: 6-[methyl(phenylsulphonyl)amino]hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1)
EC number: 248-107-3
CAS number: 26919-50-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 13/09/2013
Registered tonnage band: 100-1000

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. **Composition (Annex VI, Section 2.3.) of the registered substance;**
   - **Concentration values**
2. **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;**
3. **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;**
4. **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 2. and 3. have negative results;**
5. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**
6. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD TG 421 or 422) in rats, oral route with the registered substance;**
7. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**
8. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method 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 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 have to submit the requested information in an updated registration dossier by **11 October 2021**. You also have to 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, Hazard Assessment

[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

IDENTIFICATION OF THE SUBSTANCE

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

1. Composition of the substance (Annex VI, Section 2.3.)

"Composition of the substance" is an information requirement as laid down in Annex VI, Section 2.3 of the REACH Regulation. The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the cornerstone of all the REACH obligations. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

More specifically you identified the registered substance as a well-defined mono-constituent substance. In line with paragraph 4.3 of the Guidance for identification and naming of substances under REACH, the following applies to all mono-constituent substances, including the registered substance:

- All the impurities present at ≥ 1 % shall be identified and reported individually; and
- All the impurities relevant for the classification and/or PBT assessment shall be identified and reported individually.

For each constituent, including the main constituent and any impurity, the typical, minimum and maximum concentration level shall be specified, according to the "*Guidance for identification and naming of substances under REACH and CLP*" (May 2017, Version 2.1).

In IUCLID section 1.2 you reported the constituents with their chemical name and numerical identifiers, and typical concentration. However, ECHA has observed that the concentration ranges of the constituents (main constituent and impurities) were not reported.

ECHA therefore concludes that the compositional information has not been provided to the required level of detail, and the registration does not contain sufficient information for establishing the composition of the registered substance and therefore its identity.

You are accordingly requested to revise the information on the composition of the registered substance in order to establish a precise chemical representation of what the substance consists of, and to provide for each reported constituent (main constituent and impurities), the typical, minimum and maximum concentration levels.

Further technical details on how to report the composition of substances in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" (version 4.0, May 2017) on the ECHA website.

TOXICOLOGICAL AND ECOTOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your Grouping and read-across approach for toxicological endpoints in general before the individual endpoints (sections 2 to 7).

Grouping and read-across approach for toxicological and ecotoxicological information

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1)
- *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.)
- *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3
- screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1)
- a sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- ready biodegradability (Annex VII, Section 9.2.1.1.).

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological, ecotoxicological or fate property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration.
Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

[2] 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.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

i. Description of the grouping and read-across approach proposed by you

You consider to achieve compliance with the REACH information requirements for the registered substance 6-[methyl(phenylsulphonyl)amino]hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1) using data of structurally similar substances 6-[[(4-methylphenyl)sulphonyl]amino]hexanoic acid (EC number 278-934-5), and triethanolamine (or nitrilotriethanol, EC number 203-049-8) (hereafter the 'source' substances).

You have provided a read-across documentation in each of the endpoint summaries, and in the related CSR section, using the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: *"Read-across between the tosyl salt carboxylic acid (6 -[(p-tosyl)amino]hexanoic acid) and the registered substance is considered justified as the registered substance is manufactured directly from 6-[methyl(phenylsulphonyl)amino]hexanoic acid by simple neutralisation with triethanolamine (TEA). 6-[methyl(phenylsulphonyl)amino]hexanoic acid and 6-[(p-tosyl)amino]hexanoic acid are structural isomers. They are the same molecular weight and differ only in the position of a single methyl group. In the former, the methyl group is bound to the nitrogen atom of the sulphonamide linkage whereas in the latter, it resides on the aromatic ring. Other than ionization of the carboxylic acid group, the 6-[methyl(phenylsulphonyl)amino]hexanoic acid remains chemically unchanged upon salt formation. In water, the acid and amine components of 6-[methyl(phenylsulphonyl)-amino]hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1) dissociate completely and behave essentially as independent substances. Since TEA can be considered non-hazardous, it is the acid component of the salt that will have a more significant impact on the outcome of any (eco)toxicological or environmental tests."*
In addition, in the CSR (pages 12 and 21), you stated that [redacted].

ECHA understands that your argument relies on the fact that (1) there is similarity in chemical structure and (2) there is similarity in the physicochemical properties, and therefore you can predict the properties of the acid component of the registered substance for (eco)toxicological properties. You also argue that the registered substance dissociates into the acid and triethanolamine, and that you can predict the properties of the registered substance by reading across the properties of the dissociation products.

[3] Please see 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).

As an integral part of this prediction, you propose that one of the sources (*"the acid component of the salt")* and the registered substance (which relies on a different acid) have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

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

With regard to the proposed predictions ECHA has the following observations:

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* (version 2.1, May 2017) 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. Currently the identity of the source substances (and their impurity profile) are not detailed in the registration dossier.

ECHA notes that it is accepted that in biological conditions the registered salt will dissociate into the acid and base componsents. However for the acid component, namely (6-[methyl(phenylsulphonyl)amino]hexanoic acid), your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical properties between one of the sources (*"the acid component of the salt")* and the registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical properties does not necessarily lead to predictable or similar human health / environmental properties in other endpoints. Your justification based on structural similarity, similar physico-chemical, ecotoxicological and toxicological properties has not established why the prediction is reliable for the human health/ environmental endpoints for which the read across is claimed.

In addition, you have claimed but not demonstrated and justified with evidence, that the difference of "[...] *the position of a single methyl group"* (either bound to *"the nitrogen atom of the sulphonamide linkage"* or to the *"aromatic ring")* between the two acid components does not lead to any difference in the human health/ environmental properties. Since it is not clear whether and to what extent the two acid components are (dys)similar, ECHA considers that it is not possible to predict the properties of the registered substance from the two source substances you identified in your hypothesis.

ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects / environmental fate of the registered substance may be predicted from data of the source substances.

On that basis, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., that human health/ environmental effects may be predicted from data on some endpoints for reference substance(s), has not been met.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health/ environmental properties. As per the information available on ECHA Dissemination Portal relative to triethanolamine, there is no data suggesting that it may be hazardous. However, ECHA notes that, for your read-across to be accepted, while respecting data sharing rights of the data owner, your dossier shall contain all necessary information from the TEA studies.

Finally, Annex XI, Section 1.5 provides with regard to the reliability and adequacy of the source studies that in all cases the results of the read-across should:

- *be adequate for the purpose of classification and labelling and/or risk assessment,*
- *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),*
- *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and*
- *adequate and reliable documentation of the applied method shall be provided.*

ECHA notes that the specific considerations for the individual endpoints which result in a failure to meet the requirement of Annex XI, Section 1.5., and are set out under the endpoint concerned, see in the sections below (2 to 8).

iii. Conclusion on the read-across approach

The adaptation of the standard information requirements, namely *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1), *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2), *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3), sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.), screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1), pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) and ready biodegradability (Annex VII, Section 9.2.1.1), in the technical dossier is based on the proposed read-across approach examined above. For the reasons as set out above, ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance.

ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health/ environmental effects may be predicted from data of the source substances. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

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

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 an *In vitro* gene mutation study in bacteria (OECD TG 471, 2012) with the analogue substance(s) (6-[[(4-methylphenyl)-

sulphonyl]amino]hexanoic acid (EC number 278-934-5) and with the analogue 2,2',2''-nitrilotriethanol (or triethanolamine, EC number 203-049-8).

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected. In addition, the OECD 471, 2012 study does not provide the information required by Annex VII, Section 8.4.1., because you report in the dossier that the *"Range-finding and confirmatory assay performed with all 5 strains. Definitive assay performed with 2 strains (TA98 and TA1535)"*.
According to paragraph 13 of the current OECD TG 471 (updated 1997) at least five strains of bacteria should be used: *S. typhimurium* TA1535; TA1537 or TA97a or TA97; TA98; TA100; *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by *E.coli* WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site. The definitive assay that you have submitted used two strains. Therefore, the provided definitive assay does not meet the current guideline, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation. ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.
ECHA further notes that the documentation of the study in the dossier is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. In particular, the following elements are missing: information on used positive controls with and without metabolic activation, individual plate counts, tabular data, number of revertant colonies per plate and per negative and positive controls. Finally, no information on historical control data is provided.

Furthermore, ECHA notes that the provided supporting the study records (publications from years 1982-1986) with the analogue 2,2',2''-nitrilotriethanol (or triethanolamine, EC number 203-049-8) does not meet the requirements of a robust study summary, as defined in Article 3(28). Specifically, the endpoint study record does not provide information on positive controls with and without metabolic activation, individual plate counts, tabular data, number of revertant colonies per plate and per negative and positive controls. ECHA has provided a practical guide for "How to report robust study summaries", available at: http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf. ECHA considers there is not sufficient information to make an independent assessment of the study minimising the need to consult the full study report, and accordingly considers that for this study, you have failed to meet the requirement of Annex XI, Section 1.5. that adequate and reliable documentation of the applied method shall be provided.

As explained above, the information provided on this endpoint in the technical dossier does not meet the information requirement for the registered substance. 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information, with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14./ OECD TG 471).

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

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* micronucleus study (OECD TG 487) with the analogue 6-[[(4-methylphenyl)sulphonyl]amino]hexanoic acid (EC number 278-934-5) and three non-guideline, non GLP studies (publications with the analogue substance triethanolamine, EC number 203-049-8).

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint in the technical dossier does not meet the information requirement for the registered substance. 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 (OECD TG 473) and the *in vitro* mammalian 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.

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).

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

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* gene mutation study in mammalian cells (OECD TG 476) with the analogue substance ((6-[[(4-methylphenyl)-sulphonyl]amino]hexanoic acid (EC number 278-934-5).

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint in the technical dossier does not meet the information requirement for the registered substance. 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 tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the

thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

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 2. and 3. have negative results.

5. 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 not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

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 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) with an analogue 6-[[(4-methylphenyl)sulphonyl]amino]hexanoic acid (EC number 278-934-5).

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

Furthermore this study does not provide the information required by Annex IX, Section 8.6.2., because the exposure duration is less than 90 days and the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, there is not adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), and for this reason also, the read-across adaptation is rejected

Therefore, the information provided on this endpoint in the technical dossier does not meet the information requirement for the registered substance. 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 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. Since the substance to be tested is a waxy solid, soluble in water, ECHA concludes that testing should be performed by the oral route, using the test method OECD TG 408.

According to the test method 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: OECD TG 408) in rats.

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

"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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) with the analogue substance 6-[[(4-methylphenyl)sulphonyl]amino]hexanoic acid (EC number 278-934-5).

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint in the technical dossier does not meet the information requirement for the registered substance. 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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a waxy solid, soluble in water, 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: 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.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).
You should also carefully consider the order of testing, especially between the requested screening study (OECD TG 421/422) and the developmental toxicity study (OECD TG 414), (request 7 below) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint-specific guidance https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf, pages 461/2.

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

A "pre-natal developmental toxicity study" (test method 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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have also sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) with the analogue substance 6-[[(4-methylphenyl)sulphonyl]amino]hexanoic acid (EC number 278-934-5).

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

Furthermore the study you have submitted "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations. Therefore, there is not adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

Consequently, the information provided on this endpoint in the technical dossier does not meet the information requirement for the registered substance. Hence there is an information gap and it is necessary to provide information for this endpoint.

According to the test method 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) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a waxy solid, soluble in water, 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: OECD TG 414) in a first species (rat or rabbit) by the oral route.

8. Identification of degradation products (Annex IX, 9.2.3.)

The identification of degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX 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.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex IX, Sections 9.2 or 9.2.3. or with the general rules of Annex XI for this standard information requirement.

In the technical dossier you have not provided any standard ready biodegradability screening study with the registered substance. Instead you provided a ready biodegradation study (OECD TG 301B) with 6-[(p-tosyl)amino]-hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1) (EC number 301-097-5). The biodegradation of the test substance (test material referred as [redacted] with active ingredient content: 86.6%- water content: 13.4%) reached 76.84% after 28 days (based on theoretical CO_2 consumption) but the test failed the 10-day windows criterion.
You also provided the results of an inherent biodegradation study (OECD TG 302B) to assess the inherent biodegradability of 6-[(p-Tosyl)amino]hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1). The test was not performed on the registered substance itself but on a formulation containing the substance with excess triethanolamine and deionised water by adding 0.1825 ml/l (equivalent to 142.9 mg/l COD) of test substance to test vessels containing 357.1 mg/l of activated sludge. The biodegradability of the test material attained 78.6% based on COD after 56 days. You concluded that "*From the results of this study it can be concluded that p-TSA Triethanolamine salt does not meet the criteria for classification as 'inherently biodegradable' according to the OECD 302B method, with >70% biodegradation being achieved within the 56 day test period. The test material shows good potential for ultimate biodegradation under the conditions of this study*".

Finally, you included a citation from a published study on triethanolamine (EC number 203-049-8), where the biodegradation half-life was determined to be 0.02-0.18 days. Based on the above information, you concluded that the registered substance is readily biodegradable but fails the 10-day window.

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected. Accordingly, based on the information provided in the technical dossier, you did not demonstrate that the registered substance is readily biodegradable.

In addition, ECHA notes that you provided, under the simulation studies endpoint, two biodegradation in seawater studies (based on OECD TG 306). The first test (1996) was conducted with a formulation containing the registered substance at 2.04 mg/L, containing an excess of triethanolamine and deionised water, for which the biodegradability in seawater after 28 days reached 21.5%. You also submitted, as supporting study (2007), another degradation in seawater study (OECD TG 306) with a formulation containing 6-[(p-Tosyl)amino]hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1) containing an excess of triethanolamine and deionised water. In this study, the biodegradability attained 29.6% and 22.1% (based on COD) after 28 days with an initial test concentration of 2.5 and 3.5 mg/L, respectively.

While ECHA agrees that the marine environment is a relevant environmental compartment owing to the reported use of the registered substance (i.e., offshore oilfield drilling), the test substance used in these studies contained an excess of triethanolamine and you did not provide any quantitative information on the composition of the test material. As the information available on ECHA Dissemination Portal relative to triethanolamine suggests that it might be easily biodegraded, ECHA considers that the degradation estimates provided in these test reports might overestimate the true biodegradability of the registered substance. ECHA also emphasizes that, owing to the relatively high test concentrations used

as compared with most natural systems (and consequently an unfavourable ratio between the concentrations of test substances and other carbon sources), the OECD TG 306 is to be regarded as a preliminary test. Such test can be used to indicate whether or not a substance is easily biodegradable and is not equivalent as a simulation testing on ultimate degradation in surface water.

In summary, the formulated product containing the registered substance only achieved 21.5% biodegradability in 28 days in the OECD TG 306 test. In addition, as described previously, this figure might overestimates the true biodegradability of the registered substance (due to the presence of an excess of triethanolamine in the test substance). Accordingly, ECHA considers that the provided information support the fact that the registered substance is not easily degraded in seawater.

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable in water.

Furthermore, ECHA notes that you have not provided any appropriate justification in your CSA or in the technical dossier as to why there is no need to provide information on the degradation products. ECHA considers that this information is needed for the PBT/vPvB and risk assessments. In addition, information available on ECHA Dissemination Portal relative to the the inherent biodegradability of 6[methyl(phenylsulphonyl)amino]hexanoic acid (EC number 256-289-0) suggests that it is not easily biodegraded and that potentially persistent biodegradation products are formed.

As explained above, the information provided on this endpoint in the technical dossier does not meet the information requirements for the registered substance. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes that the design of an appropriate and suitable test method will have to be substance-specific. When analytically possible, the identification, stability, behaviour, and molar quantity of the metabolites relative to the parent compound should be evaluated. In addition, the degradation half-life, log K_{ow} and potential toxicity of the metabolite may be investigated. You will need to provide a scientifically valid justification for the chosen method.

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: Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

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 11 August 2017.

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

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

ECHA notified the draft decision to the competent authorities of the Member States for 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. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. 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.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.