Helsinki, 16 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114480977-28-01/F
Substance name: 6-[[(4-methylphenyl)sulphonyl]amino]hexanoic acid
EC number: 278-934-5
CAS number: 78521-39-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15 May 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. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

2. **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;**

3. **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;**

4. **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 **23 September 2021**. You also have to update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 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.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

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

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.

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.

In the technical dossier you have provided a study record for an *in vitro* gene mutation study in bacteria. However, this study does not provide the information required by Annex VII, Section 8.4.1., because it does not meet the requirements set up by the applicable international standard for *in vitro* gene mutation studies in bacteria.

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.

By contrast, the definitive assay that you have submitted used two strains. You report in the registration dossier that the *"Range-finding and confirmatory assay performed with all 5 strains. Definitive assay performed with 2 strains (TA98 and TA1535)".* The provided definitive assay does neither meet the current guideline requirements, as required under Article 13(3), nor can it be considered as providing equivalent data according to the criteria in Annex XI, Section 1.1.2. of the REACH Regulation, with regards to adequacy, sufficient information and validity for the endpoint being investigated. 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.

In your comments on the decision, you accepted that the OECD TG 471 study provided does not meet the current TG requirements but you note that the registered substance is neither an oxidizing mutagen nor a cross-linking agent nor hydrazine. Hence, you claim that the mutagenic potential of the test substance would have been shown in the available tests. You pointed out that there is an *in vitro* micronucleus test on human lymphoblasts available for the registered substance. According to you this is a significantly higher quality test in terms of relevance for humans, and since it is negative gives no indication of mutagenic

properties. In your opinion, the data provided on mutagenicity are sufficient to meet the information requirements.

Please note that (i) you have not explained how this comment would meet any of the criteria for an adaptation as provided by the provisions of Annex XI, and (ii) this statement is not in accordance with the requirement as set in Article 13(3) of the REACH regulation, based on which tests" *shall be conducted in accordance with the test methods laid down in a Commission Regulaton or in accordance with other international test methods recognised by the Commission or the Agency as being appropriate*".

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

ECHA 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 derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

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

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.

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.
In the technical dossier you have provided a study record for a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422). However, 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).

In your comments you claim that no further testing is necessary as you have provided an adaptation in accordance with Annex XI, Section 3, substance-tailored exposure-driven testing. In particular you indicate the following:

"*In accordance with Annex XI (3) of REACH:*
Further testing in accordance with Annex IX is omitted, based on the exposure scenario(s) developed in the Chemical Safety Report (chapter 9).
It is demonstrated and documented that all of the following conditions are fulfilled:
(i) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of all identified uses (see chapter 9 of the CSR);

(ii) DNELs (see table 19 in section 5.11.2 of the CSR/ summary in IUCLID section 7) and PNECs (Table 28 in section 7.6 of the CSR/ summary in IUCLID-Section 6) were derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement. The DNELs and PNECs were derived according to the ECHA-REACH-guidance and are relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes;
(iii) the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC (see Chapter 9 of the CSR);
Therefore, no further studies on Reproductive toxicity (Annex IX, 8.7) and on Repeated dose toxicity (Annex IX, 8.6) are necessary."

For an acceptable exposure based adaptation of Annex XI (3) all three points in section 3.2 (a) need to be fulfilled. In ECHA's view, the above mentioned information does not fulfil the points (i) and (ii) in section 3.2 (a) for the reasons set out below.

First, according to footnote 1 of REACH Annex XI Section 3.2 (a)(ii) of the REACH Regulation, the DNELs which are derived from a screening study or a 28-day study shall not be considered appropriate to omit a prenatal developmental study or a 90-day study.

The DNELs you have used are derived from a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422). Therefore, the DNELs derived from the OECD 422 study are not appropriate to omit the 90-day study and a pre-natal developmental toxicity study.

Second, according to REACH Annex XI Section 3.2 (a)(i) of the REACH Regulation the registrant should demonstrate the absence of or no significant exposure in all scenarios of the identified uses.

In the registration dossier you have calculated theoretical airborne concentration based on vapour pressure of the registered substance. This does not demonstrate the absence of or no significant exposure in all scenarios of the identified uses. The registered substance is used as a mixture ([redacted] registered substance in water mixture). Your exposure assessment does not take into account the aerolisation of the mixture, which is not dependent on vapour pressure and also dermal exposure can be relevant through splashes and spills (exposure scenarios include PROCs 3, 8a, 8b, 9 and 15).

In your comments on the decision, you also discuss the results of the existing studies (Acute toxicity and screening OECD TG 422 studies), and conclude that the effects observed are merely non-specific reactions to the extremely high doses of test substance and not the expression of a toxic effect. In your opinion repeating these tests with a larger number of animals and for 90 days instead of 53 days is not necessary as no further toxic effects are expected. You have asked ECHA to reconsider the need for a 90-day repeated dose toxicity study (B.26./OECD Test Guideline 408) on rats. Please note that your comment also does not meet the criteria for an adaptation as provided by the provisions of Annex XI nor does it meet the adaptation criteria of column 2 of Annex IX, Section 8.6.2.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on*

information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, according to the Chemical Safety Report, risk management measures are in place to prevent exposure of humans via inhalation.
Hence, the test shall 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.

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

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.

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.
In the technical dossier you have provided a study record for a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422). However, this study 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 according to OECD TG 414 like examinations of foetuses for skeletal and visceral alterations.

In your comments you claim that no further testing is necessary as you have provided an adaptation in accordance with Annex XI, Section 3, substance-tailored exposure-driven testing.

Your justification is the same as described in section 2 above for waiving the 90-day study.

Your adaptation under Annex XI, section 3 is therefore rejected for the same reasons.
In your comments on the decision, you also discuss the results of the existing study (screening OECD TG 422), and conclude that the birth of juveniles without malformations shows that there is no evidence of embryotoxicity. You asked ECHA to review the need for testing for prenatal developmental toxicity (testing method: OECD Test Guideline 414). Please note that your comment also does not meet the criteria for an adaptation as provided by the provisions of Annex XI nor does it meet the adaptation criteria of column 2 of Annex IX, Section 8.7.

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 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 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.

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

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.
The identification of the 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.

You have sought to adapt this information requirement according to Annex IX, Section 9.2.1., column 2. You provided the following justification for the adaptation: *"In accordance with column 2 point 9.2.1 of REACH annex IX, further degradation testing does not need to be conducted if a substance is classified as readily biodegradable. In Column 2 point 9.2 is written: "Further biotic degradation testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products." Based on the chemical safety assessment according to Annex I, REACH: - The substance is regarded as inherently biodegradable based on the available study results. - Further, the substance does not fulfill any of the criteria for classification according to the CLP-regulation. - Thus an exposure assessment and resulting risk characterisation is not needed. Therefore, no further degradation testing is needed."*

ECHA notes that in your adaptation you propose that it is not necessary to obtain information on the degradation products due to the fact that you claim that *"the substance is regarded as inherently biodegradable based on the available study results"* and that the registered substance *"does not fulfil any of the criteria for classification according to the CLP-regulation"*. You conclude that *"an exposure assessment and resulting risk characterisation is not needed"* and therefore you considered that the information on degradation products can be waived.

ECHA considers that the absence of classification of the registered substance in any hazard class and the fact that you did not have to provide an exposure assessment in your CSR does not provide information on the identification of degradation products itself and does not allow to take these into consideration in the PBT/vPvB assessment or the risk assessment; it is thus not a valid adaptation argument.

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. In the technical dossier, you provided the results of a biodegradation in water screening test (OECD TG 301B), which shows that ultimate degradation of the registered substance reached 25.83% in 28 days. As specified in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7b, Section 7.9.4.1. (version 4.0, June 2017), the substance is not regarded as ready biodegradable. In the robust study summary, you also mentioned that analytical monitoring (based on HPLC) revealed that < 0.1 mg/L of the registered substance was found after 28 days (where the initial concentration was 27 mg/L). You concluded that "*the test item ASC plus was degraded. Results imply that within the test period the resulting metabolites were not completely degraded based on the CO_2 development".* ECHA considers that this information indicates that potentially persistent degradation products may be formed.

You provided also the results of another biodegradation in water screening test (OECD TG 301B) with a formulated product containing 6-[(p-tosyl)amino]hexanoic acid, compound with 2,2',2''-nitrilotriethanol (1:1) (EC number 301-097-5) containing an excess of triethanolamine and deionised water. Biodegradation of the test substance reached 76.84% after 28 days (based on theoretical CO_2 consumption) but the test failed the 10-day windows criterion. Accordingly, as specified in ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b, Section 7.9.4.1.* (version 4.0, June 2017), this test substance is not regarded as readily biodegradable. In addition, ECHA notes that the test substance contains an excess of triethanolamine compared to the registered substance. As per the information available on ECHA Dissemination Portal relative to triethanolamine, it is suggested that it is easily biodegraded. Accordingly, the results reported in this study are of limited relevance and do not rule out the fact that potentially persistent degradation products may be formed.

In the chemical safety assessment (CSA), you stated that the substance is used "[redacted]". ECHA notes that you did not include any information on the end-users of these products. In addition, you specified that the registered substance is used "[redacted]" and that "[redacted]". Finally, you stated that "[redacted]". ECHA considers that the release of the substance in the environment cannot be ruled out. Based on the information provided, it seems plausible that release to municipal STP may occur during loading and/or unloading of formulations containing the registered substance as well cleaning and/or maintenance activities.

Therefore, 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 with regards to the PBT/vPvB assessment and risk assessment.

In your comments on the draft decision, you have challenged the need to generate additional information on the degradation products of the registered substance.

ECHA understands that you propose that the aminohexanoic acid moiety will undergo β-oxidation to form a γ-aminobutyric acid derivate, which will then degrade into tosylglycine through further β-oxidation. You also specified that a BUA report (BUA Substance Report No. 63 p-toluenesulphonic acid, ISBN 3-527-28447-8) concluded that p-toluenesulphonic

acid is readily biodegradable. Accordingly, the registered substance would eventually be fully mineralized despite the fact that it fails the ready biodegradability criteria (due to slow hydrolysis of the alkyl chain).

On the hypothesis you proposed, ECHA considers the following:

- The HPLC data related to the OECD TG 301B studies provide no support that the γ-aminobutyric acid derivate of ASC and tosylglycine represent the dominant (intermediary) degradation products of the registered substance. Indeed, at t = 1 day, the concentration of ASC (mean of the determination of 2 replicate flasks) was 26.9 mg/L. At t = 14 days, the concentration of ASC dropped to 1.95 mg/L, while at the same time biodegradation only reached 9.34% (based on ThCO2). This suggests that a (transient) increase in the proposed intermediary degradation products should be observed. However, over the entire period (i.e. from day 1 to day 42), the concentrations of γ-aminobutyric acid derivate of ASC and tosylglycine remained at very low levels (≤ 0.7 mg/L) and showed little variation. Accordingly, the submitted data do not support your assertion that rapid beta-oxidation during the initial stages of biodegradation leads to the measured steady state concentrations of the intermediates and neither do they act as proof of the proposed biodegradation.
- You did not provide adequate information to support that p-toluenesulphonic acid is formed as an intermediate degradation product. Additionally, you did not provide adequate information to allow ECHA to make an independent assessment of the relevance and reliability of the data used to conclude that p-toluenesulphonic acid is readily biodegradable.

ECHA concludes that the available data do not exclude that potentially persistent degradation products may be formed.

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

Regarding the design of an appropriate and suitable test method, it will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition, 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.

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 took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment. No amendments were proposed.

On 24 January 2019 you provided additional comments to the draft decision. ECHA decided to exceptionally take these comments into account for the reasons that have been communicated to you by letter dated 4 March 2019.

ECHA took into account your additional comments and did not amend the requests.

ECHA notified, again, 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 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.