EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2019

Addressee: [redacted]

Decision number: TPE-D-2114493662-40-01/F
Substance name: Sodium toluene-4-sulphonate
EC number: 211-522-5
CAS number: 657-84-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 20/12/2018
Registered tonnage band: 10 to 100 tpa [1]

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

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

1. **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 analogue substance Sodium (xylenes and 4-ethylbenzene) sulphonate (EC No. 701-037-1) specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity); and**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by ***15 September 2022***. You shall also update the chemical safety report, where relevant.

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[2] by Ofelia Bercaru, Head of Unit, Hazard Assessment

[1] There is at least a member in the joint submission, that has registered the substance at the tonnage level of 1 000 tonnes or more per year.
[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you.

Grouping of substances and read-across approach

You have submitted a testing proposal proposing to test an analogue substance, seeking to adapt information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annex X, Section 8.7.3) by applying a read-across approach in accordance with Annex XI, Section 1.5 of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the testing proposal.

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 or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances. 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.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3, 4] - (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://echa.europa.eu/publications/technical-scientific-reports

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.

A. Scope of the category

You have provided a read-across justification document in IUCLID Section 13.

You have defined the structural basis for the category/grouping as simple salts (ammonium, calcium, potassium and sodium salts) of toluene, xylene and cumene sulphonic acids.

You have identified the following substances as 'Hydrotrope' category members:

[1] Sodium toluene-4-sulphonate (EC No. 211-522-5);
[2] Sodium (xylenes and 4-ethylbenzene) sulphonate (EC No. 215-090-9[5]);
[3] Calcium (xylenes and 4-ethylbenzene) sulphonate (EC No. 248-829-9);
[4] Ammonium (xylenes and 4-ethylbenzene) sulphonate (EC No. 943-024-5);
[5] Sodium cumene sulphonate (EC No. 239-854-6);
[6] Potassium cumene sulphonate (EC No. 629-764-9); and
[7] Ammonium cumene sulphonate (EC No. 253-519-1).

i. Characterisation of the composition of the category members

The characterisation of the substances identified as members of a category needs to be as detailed as possible in order to confirm category membership and to assess whether the attempted predictions are not compromised by the composition and/or impurities. The information provided on the substance characterisation of the category members must establish a clear picture of the chemical structures of their constituents to establish the extent of qualitative and quantitative differences and similarities in the structure and in the composition of these substances. ECHA recommends to follow its Guidance for identification and naming of substances under REACH and CLP for all source substances within the category.

In Section 2.2. of the read-across justification document, you address the composition of the category members. The toluene and cumene sulphonates are mono-constituent substances whereas the (xylenes and 4-ethylbenzene) sulphonates are UVCB substances. Toluene-, cumene- and 4-ethyl- benzene sulphonate are mainly in the from of the para-isomer (approximately [redacted] For xylene-benzene sulphonate the alkyl groups are mainly in the [redacted]

ECHA considers the information with regard to the composition of the category members as sufficient in order to establish structural similarity (and structural differences) between the category members.

ii. Applicability domain of the category

[5] The current EC number for this substance is 701-037-1.

According to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.4.1, (version 1.0, May 2008) a category hypothesis should address *"the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint. These rules, can be described as the applicability domain for an endpoint and provide a means of extending the category membership to chemicals not explicitly included in the current definition of a category."*

Furthermore, according to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.1.2, (version 1.0, May 2008) *"a category evaluation does not necessarily result in all the individual substances included in the category evaluation being registered to the Agency, although the data from these substances will be included in the category report in support of the registration."*

Based on your description of the structural basis of your grouping/category approach, ECHA understands that all category members share a common 'core structure' and that they vary only in terms of their alkyl- substitutions on the benzene ring. Furthermore, ECHA understands that the allowed substituents to the 'core structure' define the inclusion critera for the category membership. You have described the applicability domain of the category as ammonium, calcium, potassium and sodium salts of cumene, toluene, and xylene sulphonic acids.

Considering the UVCB nature of the (xylene and 4-ethylbenzene) sulphonate, ECHA considers that the applicability domain of the category to be: ammonium, calcium, potassium and sodium salts of cumene, toluene, and xylene (containing up to [redacted] ECHA notes that the category consists of ammonium, calcium, potassium and sodium salts of cumene-, toluene- and xylene (containing up to [redacted] The structural variation within the category is defined by the type of cation and which sulphonic acid that forms the anion. Because ECHA accepts read-across between the ammonium, calcium, potassium and sodium salts of each individual sulphonic acid provided that the source study is adequate and reliable for the endpoint concerned, the structural variation within this group is defined by the sulphonic acid used; i.e. cumene-, toluene-, and xylene (containing up to [redacted] ECHA assessed your proposed predictions on this basis.

B. Prediction of toxicological properties

You have provided the following reasoning for the prediction of toxicological properties: *"The Hydrotrope category comprises seven substances which have similar chemical structures and demonstrate the same type of effects. [...] The same absence of or type of effect are observed for the different source substances. There are no relevant variations in the strength of the effects observed among the source substances and the same strength is predicted for the target substances".*

ECHA understands that you base your predictions on the assumption that different compounds have similar toxicological properties as a result of structural similarity. You assume that all substances will show the same absence of or type of effects for toxicological properties. ECHA notes the following shortcomings with regards to prediction of toxicological properties:

i. *Insufficient information to support a claim of the* same absence of or type of effects *toxicological properties*

According to Annex XI, Section 1.5., *'Application of the group concept requires that [...] human health effects [...] may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).'*

A number of factors contributes to the robustness of the predictions made within a group. According to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.1.5. (version 1.0, May 2008), one of these factors is the density and distribution of the available data across the category. In order to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.

In the read-across hypothesis, you assume the same absence of or type of effects across the category. You argue that this is supported by the available studies on the various category members which demonstrate similar toxicity.
You have provided:

- Repeated dose toxicity studies with (xylenes and 4-ethylbenzene) sulphonate, toluene sulphonate and sodium cumenesulphonate;
- Pre-natal developmental toxicity studies in rats and rabbits conducted with (xylenes and 4-ethylbenzene) sulphonates;
- Reproductive and developmenal toxicity screening test conducted with toluene sulphonate;
- *In vitro* mutagenicity studies conducted with Sodium (xylenes and 4-ethylbenzene) sulphonate;
- *In vivo* micronucleus test and a sub-chronic toxicity study with Calcium (xylenes and 4-ethylbenzene) sulphonate and Sodium cumene sulphonate; and supporting toxicokinetic information available on toluene sulphonate.

ECHA notes that you predict (or propose to predict) the toxicological properties of the cumene- and toluene- sulphonates from the available data (or data to be generated on) (xylenes and 4-ethylbenzene) sulphonates thus the information available does not cover the range of structural variations. However, there is very little data available on the target substances to support such a prediction for the human health endpoints of mutagenicity, developmental toxicity and toxicity to reproduction.

With regard to reading across from a (xylenes and 4-ethylbenzene) sulphonate to the toluene sulphonates (and *vice versa*), ECHA notes that the results from the available reproductive and developmental toxicity screening test conducted with a toluene sulphonate is consistent with the available repeated dose toxicity and pre-natal developmental toxicity studies conducted with the (xylenes and 4-ethylbenzene) sulphonates. In both cases, a lack of toxicity has been demonstrated up to the limit dose.
In addition, there is supporting toxicokinetic information available on toluene sulphonate which demonstrates that this substance is excreted unchanged in urine.
Therefore, ECHA considers it likely that the toxicity to reproduction effects of toluene sulphonates may be predicted from (xylenes and 4-ethylbenzene) sulphonates or *vice versa*.

C. Conclusions

ECHA accepts read-across between the ammonium, calcium, potassium and sodium salts of toluene- and (xylene and 4-ethyl benzene)- sulphonic acid; provided that the source study is adequate and reliable for the endpoint concerned.

Reading across form (xylene and 4-ethyl benzene) sulphonates to toluene sulphonate (and *vice versa*), for toxicity to reproduction "bridging information" is available and as a result ECHA considers the proposed read-across as plausible. The validity of the read-across approach will be re-assessed once the requested information has been submitted in an dossier update; if this information confirm the read-across approach and its plausibility, the read-across approach can (only) then be accepted.

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

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

Examination of the testing proposal

The basic test design of an extended one-generation reproductive toxicity study (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 of the REACH Regulation. 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 in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to OECD TG 443 by the oral to be performed with the analogue substance Sodium (xylenes and 4-ethylbenzene) sulphonate (EC No. 215-090-9[6]) with the following justification and specification of the study design:

- *"The standard 10 week premating exposure is proposed;*
- *Administration via oral route is proposed;*
- *1000 mg/kg/day is proposed as the highest dose for the study;*
- *Extension of Cohort 1 B is not justified. There is exposure to consumers and professionals, however, extension of Cohort 1 B to produce the F2 generation is not justified because: the substance is not classified as Muta. 1A or 1B or 2; There is no indications that the substance reach steady state only after prolonged exposure (i.e. substance is not PBT of vPvB; Log P_{ow} is -1.1); and 'there are no indications based on available study results that endocrine disruption is a relevant mode of action, additionally no structural alerts exists'.*
- *Inclusion of Cohorts 2A and 2 B is not justified. "This is based on:*
    - *previous studies with the substance do not indicate neurotoxic effects such as changes in brain weight or in specific neural areas not secondary to body weight, changes in brain volume or specific neural areas or (histo)pathological findings in brain, spinal cord and/or nerves*
    - *test animals exposure to the substance have not expressed any behavioural changes in the absence of general toxicity*
    - *the substance is not known to have any mode of action associated with neurotoxicity such as cholinesterase inhibition and thyroid toxicity*

[6] The current EC number for this substance is 701-037-1.

- *there are no indications that endocrine disruption is a relevant mode of action for the substance*
- *no structural analogues are known to show neurotoxic effects* "; and

- Inclusion of Cohort 3 is not justified. *"This is based on:*
  - *the substance has not caused biologically significant changes in haematology/clinical chemistry and/or organ weight associated with immunotoxicity such as reduced leucocyte count in combination with reduced spleen weight in repeated dose studies*
  - *the substance has not caused significant effects to immunology organs such as thymus atrophy in repeated dose studies*
  - *the substance is not classified as a (respiratory) sensitizer*
  - *there are no indications that endocrine disruption is a relevant mode of action for the substance*
  - *no structural analogues are known to show immunotoxic effects".*

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to column 1 of Section 8.7.3., Annex X is required. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed 10 weeks premating exposure duration and 1000 mg/kg/day as the highest dose for the study.

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*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and 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 relevant data to be used for dose level setting, it is recommended that results from a 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.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed not to include an extension of Cohort 1B and provided justifications taking into account the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA agrees that the criteria to extend the Cohort 1B are not met and concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of Section 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You proposed not to include Cohorts 2A and 2B and provided justifications taking into account the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA agrees that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

You proposed not to include Cohort 3 and provided justifications taking into account the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA agrees that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

Species and route selection

You proposed testing in rats. According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

You proposed testing by the oral route. ECHA agrees 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, ECHA concludes that testing

should be performed by the oral route.

Comments on the draft decision

In your comments you agreed to perform the requested study.

Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the analogue substance or Sodium (xylenes and 4-ethylbenzene) sulphonate (EC No. 701-037-1): Extended one-generation reproductive toxicity study (test method 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 systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity); and
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Appendix 2: Procedural history

There is one member in the joint submission, which has registered the substance at the tonnage level of 1000 tonnes or more per year.

This draft decision replaces the previous draft decision with Communication number: TPE-D-2114319217-54-01/D.

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 10 November 2016.

ECHA held a third party consultation for the testing proposals from 22/06/2017 until 07/08/2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **11 March 2019**, 30 calendar days after the end of the commenting period.

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

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and your updated dossier and did not amend the request.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of the Member States.

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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.