EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2019

Addressee: [redacted]

Decision number: CCH-D-2114493648-30-01/F
Substance name: TOLUENE-4-SULPHONIC ACID
EC number: 203-180-0
CAS number: 104-15-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/08/2018
Registered tonnage band: Over 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 or its sodium salt;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the sodium salt of the registered substance provided that the study requested under 1. has a negative result;**

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method OECD TG 443) in rats, oral route with sodium (xylenes and 4-ethylbenzene) sulphonates (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);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

4. **Identification of PNEC (Annex I, Section 3.3.1.): revise PNECs for freshwater, marine water, intermittent releases, freshwater sediment and marine sediment - using the study giving rise to the highest concern according to Annex I, Section 3.1.5.**

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.

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.

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## 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 Wim De Coen, 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**

**INFORMATION ON TOXICOLOGY AND ECOTOXICOLOGY**

**I. Grouping and read-across approach for (eco)toxicological information**

Your registration dossier contains adaptation arguments which are based on a grouping and read-across approach in accordance with Annex XI, Section 1.5. of the REACH Regulation. You have grouped registered substances and formed a group (category) of 'aromatic sulphonic acid' to predict from data for reference substance(s) missing (eco)toxicological properties for other substances within this group (read-across approach).

You seek to adapt the information requirements for the following standard information requirements by grouping substances in the category and applying a read-across approach in accordance with Annex XI, Section 1.5:

i. *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.);
ii. *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.);
iii. sub-chronic toxicity study (90-days; Annex IX, Section 8.6.2.);
iv. pre-natal developmental toxicity study (Annex IX, Section 8.7.2.); and
v. pre-natal developmental toxicity study (Annex X, Section 8.7.2.).
vi. Short-term toxicity testing on invertebrates (Annex VII, Section 9.1.1);
vii. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2);
viii. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3);

ECHA has considered the scientific and regulatory validity of your grouping and read-across approach in general before assessing the individual properties of the substance in section II of this appendix.

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[2, 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.

A. Scope of the category

You have provided a read-across justification document in the CSR (sections 0.1 and 0.2).

You have defined the structural basis for the category/grouping as "*sulphonic acids, a class of organic acids with the general formula R-S(=O)$_2$-OH, where* R "

You have identified the following substances as the 'Aromatic Sulphonic Acids (ASA)' category members:

[1] Toluene-4-sulphonic acid (EC No. 203-180-0, CAS No. 104-15-4);
[2] 2 (or 4)-toluene sulphonic acid (EC No. 274-893-2, CAS No. 70788-37-3);
[3] (Xylenes and 4-ethylbenzene) sulphonic acid (EC No. 701-247-3, CAS No. NS);
[4] Benzene sulphonic acid (EC No. 202-638-7, CAS No. 98-11-3);
[5] p-cumene sulphonic acid (EC No. 240-210-1, CAS No. 16066-35-6);
[6] Cumene sulphonic acid (EC No. 253-730-9, CAS No. 37953-05-2);
[7] Hydroxybenzensulphonic acid (EC No. 215-587-0, CAS No. 1333-39-7) and
[8] 4-hydroxybenzene sulphonic acid (EC No. 202-691-6, CAS No. 98-67-9).

The substances are hereafter refered to as substance [1] to [8].
In your comments to the draft decision you discuss in further detail the similarity between the members of your category. You state, for example, that

- it has been concluded in different reports that sulfonic acids behave in a toxicologically similar manner and that para-TSA (toluene sulphonic acid) can be used as a toxicological surrogate for BSA (benzene sulphonic acid).
- you acknowledge a slight increase of activity from BSA to CSA (cumene sulphonic acid) due to the alkyl substituents, which can increase the nucleophilicity of the benzene ring. However, you consider it negligible.

[2] 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)
[3] 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

- the increase in carbon atoms from toluene to xylene and to cumene improve solubility in apolar solvents and reduce solubility in polar solvents like water. You state that the substances are highly water-soluble and expected to be rapidly excreted and minimally absorbed into systemic circulation.
- the substances have low octanol-water partitioning coefficients (Kow). Therefore, you indicate that they have similar behaviour in the environment due to their affinity for water phase and that bioaccumulation is not expected.
- the reactivity increases from the substance with the lowest acidity (HBSA; hydroxybenzene sulphonic acid) to the one with highest acidity (CSA) and therefore you consider that CSA and HBSA could be considered as the most representative substances of the group for the evaluation of human health effects and environmental distribution properties.
- HBSA could be considered one of the metabolites of BSA since usually the aromatic hydroxylation is the first reaction in the microbial and human metabolism (confirmed by the available data on TSA). Therefore, you say that HBSA has the highest water solubility and is the lowest bioavailable and CSA has the highest number of methyl groups with the most activated benzene ring.

You further provide information from the QSAR Toolbox, showing for example that there are no alerts for genotoxicity for any of the members of the category (or any of their corresponding salts), and that alerts for reprotoxicity are similar for the aromatic sulphonic acids and the hydrotropes.

*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.

You have not addressed the composition of the category members in your read-across justification. However, information on composition for substances [1], [3], [4], [5] and [8] can be found in the IUCLID dossiers for the respective registrations.

The toluene-4, benzene, 4-hydroxybenzene and p-cumene sulphonic acids are mono-constituent substances whereas the (xylenes and 4-ethylbenzene) sulphonic acid is an UVCB substance.

Toluene-4, p-cumene- and 4-ethyl-benzene sulphonic acids are mainly in the form of [redacted] For xylene-sulphonic acid the alkyl groups are mainly in the [redacted]

ECHA considers the information provided in the technical dossiers with regard to the composition of the category members [1], [3], [4], [5] and [8] as sufficient to establish structural similarity (and structural differences) between the category members.

However, substances [2], [6] and [7] are not registered under REACH. Therefore, no information on their composition is available. As a consequence, ECHA considers that there is

no adequate information available to establish the extent of the similarity and of the differences in the structure and in the composition of these three substances.

*ii. Applicability domain of the category*

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 defined the structural basis for the category/grouping as "*sulphonic acids, a class of organic acids with the general formula R-S(=O)$_2$-OH, where R is usually a hydrocarbon (aromatic) side chain*".

Considering the UVCB nature of the (xylene and 4-ethylbenzene) sulphonic acid, ECHA considers that the the applicability domain of the category to be: sulphonic acids of benzene, hydroxybenzene, cumene, toluene, and xylene (containing up to [redacted] 4-ethylbenzene). The structural variation within the category is defined by the alkyl- (or hydroxy-) substituents on the core structure, i.e. benzene sulphonic acid. 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 acidity of the sulphonic acid group is not expected to change significantly among the five aromatic sulphonic acids.[.....] Thus the reactivity of the sulphonic acids are very similar and they can each be used as a surrogate for the others. A full set of 2010 guideline physical-chemical studies demonstrates the similar chemical and physical properties and behavior of the 5 sulphonic acids in the category. The sulphonic acid moiety is the primary driver for mammalian toxicity and any difference between the benzene, xylene, cumene, and toluene moieties would be insignificant given the relatively high level of corrosivity of all five substances in the category.*"

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 type of effects for toxicological properties. ECHA notes the following shortcomings with regards to prediction of toxicological properties:

*i. Insufficient information to support the claim of the* same type of effects *for 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, based on the available information, the same type of effects across the category. You provided:

- Repeated dose toxicity studies conducted with a (xylenes and 4-ethylbenzene) sulphonate and p-toluene sulfonic acid
- pre-natal developmental toxicity studies conducted with a (xylenes and 4-ethylbenzene) sulphonates in rats and rabbits;
- Reproductive and developmenal toxicity screening test conducted with p-toluene sulfonic acid as well as supporting toxicokinetic information available on toluene sulphonate; and
- In vivo micronucleus test with cumene sulphonate and calcium xylenesulphonate
- In vitro micronucleus tests with p-toluenesulfonic acid
- In vitro gene mutation study in bacteria with benzenesulfonic acid and p-toluenesulfonic acid (both studies not acceptable due to quality issues as described in section II)

ECHA notes that you predict (or propose to predict) the properties of the members of the category from data available mainly on (xylenes and 4-ethylbenzene) sulphonates and its salts, and to a lesser extent on toluene-4 sulphonic acid and its corresponding salt and on p-cumene sulphonate. Prediction is based on structural similarity and appears plausible if the available data allows for a side-by-side comparison of the toxicity profiles of the source and target substance.

However, there is very little data available on the target substances benzene, p-cumene and hydroxybenzene sulphonic acids to support such a prediction for the endpoints of mutagenicity, repeated dose toxicity, developmental toxicity and toxicity to reproduction. Therefore, ECHA considers that the available information does not cover the range of structural variations for those substances and hence there is no support for your claim of a regular pattern of similar ecotoxicological properties.

With regard to reading across from (xylenes and 4-ethylbenzene) sulphonic acid or sulphonate to toluene 4-sulphonic acid (and *vice versa*), ECHA notes that the results from the available reproductive and developmental toxicity screening test conducted with toluene sulphonic acid is consistent with the available repeated dose toxicity and pre-natal developmental toxicity studies conducted with (xylenes and 4-ethylbenzene) sulphonates. In both cases a lack of toxicity have been demonstated 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 repeated dose, developmental toxicity and the toxicity to reproduction effects of toluene sulphonates may be predicted from (xylenes and 4-ethylbenzene) sulphonates. This conclusion is further supported by a 28-day repeated dose toxicity study on toluene 4-sulphonic acid. However, for mutagenicity there is not a sufficient database to allow for a side-by-side comparison of the effects. Therefore, ECHA considers that, in the absence of any relevant mutagenicity data on toluene sulphonic acid, the available information does not support your claim of a regular pattern of same type of effects for with regard to mutagenicity. This issue is further discussed below and under the respective endpoints for genotoxicity.

With regard to reading across from a (xylenes and 4-ethylbenzene) sulphonate or toluene sulphonic acid to the p-cumene, benzene, and hydroxybenzene sulphonic acids (and *vice versa*) first for human health endpoints other than mutagenicity, ECHA notes that there is no relevant information to allow a side-by-side comparison of effects related to repeated dose toxicity, reproductive or developmental toxicity wich supports the read-across approach. Furthermore, there is no toxicokinetic information available on the substances that could have helped supporting the read-across approach.

Therefore, in the absence of any relevant repeated dose, reproductive or developmental data on p-cumene, benzene, and hydroxybenzene sulphonic acids, ECHA considers that there is no support for the read-across for these endpoints. A reproductive and developmental toxicity screening test (OECD TG 422) allows a screening level assessment of such effects and could potentially be used to support read-across for these endpoints, provided that the results obtained are consistent with those obtained with the source substances.

Secondly, for mutagenicity, ECHA notes that for p-toluenesulfonic acid, a xylenesulphonate, and a cumene sulphonate, that there are *In vitro* and *In vivo* micronucleus tests available. However, the *In vitro* tests for mutagenicity cover two aspects, chromosome aberration and gene mutation. There is no acceptable information available which would allow comparison of the gene mutation potential between these category members. In the absence of such data, ECHA considers that there is no support for your claim of a regular pattern of same type of effects with regard to potential to induce gene mutation for any of the category members.

Furthermore, for benzene sulphonic acid and hydroxybenzene sulphonic acid, there is no acceptable data available on chromosome aberration. In the absence of suitable "bridging information", ECHA considers that there is no support for your claim of a regular pattern of same type of effects with regard to that endpoint for benzene sulphonic acid and hydroxybenzene sulphonic acid.

ECHA has evaluated the information from QSAR Toolbox provided by you. We note that the lack of experimental results for many endpoints is a concern in this case. Generally, the purpose of QSAR Toolbox is to group substances with similar structures and profiling outcome to fill the data gaps with available experimental data. In this particular case, it appears this group of substances was grouped mainly on the basis of similar physical, structural and chemical properties, and consistent outcome from the QSAR Toolbox profilers within the group. The profilers are only indicative additional 'similarity measures'. Therefore the consistency within the profiling outcome have to be confirm by the consistency of the data from toxicological studies, and consequently reliable experimental data for category members must be available. Taking these considerations into account, this QSAR Toolbox category can be considered as a good starting point for category formation, but the available information is not sufficient to predict consistent toxicological behaviour of the category members.

In conclusion, ECHA considers that there is still no support for your claim of a regular pattern of same type of effects for the endpoints discussed above due to missing "bridging" information. In your endpoint-specific comments generation of such information is discussed, and ECHA has responded to those comments below under the respective endpoint requests.

C. Prediction of ecotoxicological properties

You have provided the following reasoning for the prediction of ecotoxicological properties: *".....the acidity of the sulphonic acid group is not expected to change significantly among the five aromatic sulphonic acids. [.....] Thus the reactivity of the sulphonic acids are very similar and they can each be used as a surrogate for the others. A full set of 2010 guideline physical-chemical studies demonstrates the similar chemical and physical properties and behavior of the 5 sulphonic acids in the category.[...] The aromatic sulphonic acids are almost completely ionized in watery environments."*

ECHA understands that you base your predictions on the assumption that different compounds have similar ecotoxicological properties as a result of structural similarity. ECHA notes the following shortcomings:

*i. Insufficient information to support a claim of similar ecotoxicological properties*

According to Annex XI, Section 1.5., *'Application of the group concept requires that [...] environmental effects or environmental fate 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.

*Ecotoxicological properties*

In the read-across hypothesis, you assume similar ecotoxicity properties across the category.

ECHA notes that you propose to predict the properties of the members of the category from data available mainly on toluene-4-sulphonic acid, on salts of (xylenes and 4-ethylbenzene) sulphonic acid, and on benzene sulphonic acid. However, based on the information provided in the technical dossier of category members, there is very little data available on the category members to support such a prediction for the aquatic toxicity endpoints of algae growth inhibition, short-term toxicity testing on aquatic invertebrates, and short-term toxicity testing on fish, as explained below:

- short-term toxicity testing on fish: data is only available for one member of the category, toluene-4-sulphonic acid.

- short-term toxicity testing on aquatic invertebrates: one reliable study is available for one member of the category, benzene sulphonic acid (key study). A study is available also on toluene-4-sulphonic acid, but with an exposure duration of 24h ('weight of evidence' study). According to the ECHA guidance R7b (Section R.7.8.4.1), 24 hour

values can have considerable variability in the repeatability of results and should not be compared to 48 hour values. Therefore ECHA considers that this study on toluene sulphonic acid cannot be used to compare with the study on benzene sulphonic acid.

- algae growth inhibition: meaningful data for comparison are available only on two category members, i.e. toluene-4-sulphonic acid and (xylenes and 4-ethylbenzene) sulphonic acid. There is also an algae study available for benzene sulphonic acid (key study), but the study has not been performed in optimal pH conditions (i.e. pH of 3 and 5 at the two highest test concentrations, which might have influenced the results), hence its results cannot be compared to those of studies with the other two category members.

Consequently, the data density across the category members is limited in the aquatic toxicity endpoints. In particular, for 4-hydroxybenzene sulphonic acid and p-cumene sulphonic acid, no aquatic toxicity data is available. With such limited reliable information available on the aquatic toxicity, no quantitative trend between the category members can be established for these endpoints.

Therefore, ECHA considers that the available information does not cover the range of structural variations and hence there is no support for your claim of a regular pattern of similar ecotoxicological properties.

In response to the additional information provided in your comments on the draft decision, you acknowledge that no tests are available for 4-hydroxybenzene sulphonic acid and you indicate that new tests will be performed in order to strengthen the validity of the category. In your endpoint-specific comments generation of such information is discussed.

Furthermore, you consider that the read-across between toluene-4-sulphonic acid and benzene sulphonic acid is acceptable and you claim that the presence of methyl group on the benzene rind does not significantly impact the ecotoxicological profile of the substance. However, ECHA notes that you do not provide any evidence to support your claim.

In particular, ECHA considers that there is still no support for your claim of a regular pattern of same type of effects for the endpoints discussed above due to missing "bridging" information. As a consequence, ECHA notes that the read-across between 4-hydroxybenzene sulphonic acid and benzene sulphonic acid, as well as, benzene sulphonic acid and toluene-4-sulphonic acid is not acceptable based on the information currently available.

ECHA acknowledges that in your comments on the draft decision you indicate your intention to strengthen the read-across approach after new data for the registered substance (or its corresponding salt) become available. However, you do not specify which substance you want to test in the long-term studies. Since this information and an updated read-across justification for the long-term aquatic toxicity endpoints is not yet available, ECHA cannot currently assess whether your choice of appropriate tests and use read-across adaptations for the long-term aquatic toxicity endpoints would be acceptable.

ECHA will evaluate your information after the deadline of this decision according to the specific rules of column 2 adaptations in Annex IX/X, and in support of an adaptation according to Annex XI, section 1.5.

For your consideration, ECHA notes there may be information available on these substances that has not been included in the technical dossier nor in the data matrix for ecotoxicity even

though such data may be relevant. For instance, in your read-across justification you propose read-across between each individual sulphonic acid and the corresponding ammonium, calcium, potassium and sodium salts (defined as "hydrotropes" or "sulphonates" in your read-across justification document). However, ECHA notes that there are aquatic toxicity studies available in the technical dossiers of the corresponding salts that have not been considered and reported in the technical dossier of the acid (e.g. short-term fish and short-term *Daphnia* studies on (xylenes and 4-ethylbenzene) sulphonate, short-term *Daphnia* study on sodium toluene sulphonate). Since these additional studies on salts have not been included in the technical dossiers of the registered substance, they could not be taken into account when assessing the scientific and regulatory validity of your grouping and read-across approach of the 'aromatic sulphonic acid (ASA) ' category.

D. Conclusion

ECHA accepts read-across between the "aromatic sulphonic acids" and their corresponding ammonium, calcium, potassium and sodium salts provided that the source study is adequate and reliable for the endpoint concerned.

- *Read-across for toxicological endpoints*

Reading across from (xylene and 4-ethyl benzene) sulphonates to toluene sulphonic acid (and *vice versa*), for repeated dose toxicity, developmental toxicity and toxicity to reproduction "bridging infromation" is available and as a result ECHA accept the proposed read-across. However, ECHA considers that due to missing "bridging infromation" it is not possible to establish a scientifically credible link between the target and source substances which would allow to predict the outcome of the *in vitro* mutagenicity tests. Concequently, read-across is rejected for mutagenicity.

Reading across from (xylene and 4-ethyl benzene) sulphonates and toluene sulphonic acid to p-cumene, benzene, and hydroxybenzene sulphonic acids (and *vice versa*), ECHA considers that due to missing "bridging information" it is not possible establish a scientifically credible link between the target and source substances which would allow to predict the outcome of the *in vitro* mutagenicity tests, repeated dose toxicity, developmental toxicity studies, and toxicity to reproduction studies. Concequently, read-across is rejected for these endpoints.

For benzene sulphonic acid and hydroxybenzene sulphonic acid, read-across for chromosome aberration is furthermore rejected in the absence of suitable "bridging information".

- *Read-across for ecotoxicological endpoints*

ECHA considers that due to missing "bridging information" it is not possible to establish a scientifically credible link between the category members which would allow to predict the outcome of the algae growth inhbition, short-term fish and short-term *Daphnia* studies. Consequently, the proposed read-across is rejected.

**II. Specific considerations on the information requirements**

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

## 1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

In the technical dossier you have provided the following study record:

1. Key study for the registered substance p-toluenesulfonic acid (EC no 203-180-0) according to OECD TG 471, (*in vitro* gene mutation study in bacteria rel. 2, GLP compliant, 1988, [redacted])

You have also sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following study record:

2. Supporting study for the analogue substance [redacted] no guideline specified (*in vitro* gene mutation study in bacteria, rel.2, non-GLP compliant, 1988, [redacted] publication)

However, as explained above, your adaptation of the information requirement is rejected.

According to paragraph 13 of the current OECD TG 471 test guideline (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 two studies you have provided were performed in 1988 according to OECD TG 471 and no guideline, respectively. The studies have an assigned reliability score of 2. Study [1] used five different strains of *S. typhimurium* [TA 1535, TA 1537, TA 1538 TA 98 and TA 100] and study [2] used four different strains of *S. typhimurium* [TA97, TA98, TA100, TA1535] but in both studies strains of *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) were not included. Since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is now required. Additionally, study [1] lacks for the strains TA100, TA1535 and TA 1537 the metabolic activation for the positive controls. Furthermore, in study [2] metabolic activation was only used in the highest dose which is not according the the standard test guideline.

Therefore, the studies do not provide the information required by Annex VIII, Section 8.4.1. and the information provided on this endpoint for the registered substance in the technical

dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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

In your comments to the draft decision you propose to cover the data gap for this endpoint with an available test with sodium toluene sulphate and with new test performed on benzene sulfonic acid and cumene sulfonic acid. ECHA notes that the quality of the available test will be evaluated during follow-up according to Article 42.

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

**2. 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.

ECHA notes that the registration dossier does not contain study records or adaptataions according to Column 2 of Annex VIII, Section 8.4.3. or according to Annex XI for this endpoint. Adequate information *on in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that the studies requested under [1] and [2] have negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

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.

In your comments to the draft decision you agree to perform this test on the sodium salt of the registered substance. ECHA agrees on that approach.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the sodium salt of 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 the study requested under [1] has a negative result.

**3. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)**

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2

generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

*a) The information provided*

In the technical dossier you have provided a study record for a "reproduction/developmental toxicity screening test" (test method: OECD TG 421) with the registered substance. However, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.

Therefore, your adaptation of the information requirement is rejected.

Furthermore, you have sought to adapt the information requirements for this endpoint by providing the following justifications:

*"Studies from the chemically related hydrotropes category are being recommended as read across for this endpoint. Hydrotropes are the salt form of the sulphonic acids. The corrosive nature of the sulphonic acids with regard to animal welfare further support this waiver. The 90-day oral rat and oral mouse studies and the 2-year chronic dermal rat and mouse studies with the closely related hydrotropes included examination of sex organs of both sexes. No treatment related effects were observed on reproductive organs."*

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2.(*Weight of evidence*).

You have furthermore sought to adapt this information requirement by providinga a waiver that could be interpreted as an adaptation according to Annex XI, Section 3. of the REACH Regulation (*Exposure-based waiving*):

*"The study does not need to be conducted because relevant human exposure can be excluded as demonstrated in the relevant exposure assessment".*

These two adaptations are evaluated below.

*Weight of evidence*

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study provides, in addition to information to general toxicity, information in particular on two aspects, namely on sexual function and fertility in P0 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to pre- and postnatal and adult exposure in the F1 generation (further referred to as 'effects on offspring').

Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after sufficient pre-mating exposure duration and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood including investigations to detect certain endocrine modes of action, and sexual development. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' needs to be considered.

ECHA notes that the studies referred to in your adaptation may provide information on systemic toxicity. However, none of the studies are studies intended to investigate "sexual function and fertility" or "developmental toxicity". Thus, the studies do not provide sufficient information to conclude on these aspects of an extended one-generation reproductive toxicity study.

ECHA concludes that your justification for the adaptation do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3. Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

*Exposure-based waiving*

According to Article 13(1) and Section 3 of Annex XI of the REACH Regulation, testing in accordance with Annex IX may be omitted based on a thorough and rigorous exposure assessment, provided that any one of the three criteria of Section 3 of Annex XI is met and adequate justification and documentation is provided.

The first criterion 3.2(a) requires "*absence of or no significant exposure in all scenarios of the manufacture and all identified uses*". In several exposure scenarios for the combined routes, systemic long-term the RCRs values are above [redacted] In addition, the used PROCs indicate potential for exposure (for example PROCs 10 and 11). ECHA considers that adequate and reliable documentation demonstrating the "*absence of or no significant exposure in all scenarios of the manufacture and all identified uses*" has not been provided.

The second criterion 3.2(b) requires a demonstration that "*throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f)*" apply. As mentioned above, in several exposure scenarios for the combined routes, systemic long-term the RCRs were not demonstrating strictly controlled conditions as per Annex XI, section 3.2 (b). Strictly controlled conditions are not demonstrated and therefore criterion 3.2(b) for exposure-based adaptation is not satisfied. In particular, condition (a) as set out in Article 18(4) does not

appear to be fulfilled because it has not been demonstrated that the substance is rigorously contained by technical means during its whole lifecycle.

Therefore, your adaptation of the information requirement is rejected.

*Conclusion*

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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

*b) The specifications for the study design*

*Premating exposure duration and dose-level setting*

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* 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 a range-finding study (or range finding studies) is performed and that its results are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

*Species and route selection*

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

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

c) Comments on the draft decision

In your comments to the draft decision you propose to use read-across from the new OECD 443 test on sodium xylene sulphonates (EC no. 701-037-1) to cover this endpoint. ECHA agrees to this approach provided that the read-across is sufficiently justified.

d) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with sodium xylene sulphonate: 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);
- 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.

## 4. Identification of PNEC (Annex I, Section 3.3.1.): revise PNECs for freshwater, marine water, intermittent releases, freshwater sediment and marine sediment - using the study giving rise to the highest concern according to Annex I, Section 3.1.5.

In accordance with Articles 10(b) and 14(1) of the REACH Regulation, the registration must contain a chemical safety report (CSR) which documents the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I to the REACH Regulation.

Annex I, Section 3.3.1. of the REACH Regulation requires to establish a PNEC for each environmental sphere based on the available information.

Further, pursuant to Annex I, Section 3.3.2. if it is not possible to derive the PNEC, then this shall be clearly stated and fully justified.

For the calculation of PNEC aquatic you have used a study on the analogue substance benzene sulphonic acid according to OECD TG 201 (Alga, growth inhibition test): [redacted] as the key study. ECHA notes that you have sought to adapt the information requirement for growth inhibition study aquatic plants according to Annex XI, Section 1.5. of the REACH Regulation. However, as explained above, your adaptation of the information requirement according to Annex XI, Section 1.5. is rejected. In additon, ECHA notes further that this read-across study is not adequate to conclude on this endpoint because, contrary to what is stated in the OECD TG 201, the concentration used in this limit study (i.e. 73 mg a.i./L) is below the threshold of 100 mg/L of active substance. Thus, this study does not provide the information required by Annex VII Section 9.1.1.. Therefore, this read-across study cannot be used to derive a reliable PNEC aquatic for the registered substance.

Consequently, the information provided on PNEC for the registered substance in the chemical safety report does not meet the general requirements for preparing a chemical safety report as described in Annex I, Section 3.3.1.

In your comments to the draft decision you agree with this request. You indicate that you will re-evaluate the available studies in order to re-calculate PNEC values and perform a new risk assessment.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to revise PNECs for freshwater, marine water, intermittent releases, freshwater sediment and marine sediment - using the valid study on the registered substance and/or its corresponding salt and giving rise to the highest concern according to Annex I, Section 3.1.5.

## 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 24 July 2018.

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 amended the requests.

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

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

## 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 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.

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 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.