

Helsinki, 18 May 2020

**Addressees**

Registrant(s) of JS\_ N-butylbenzenesulphonamide as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**

9 September 2019

**Registered substance subject to this decision ("the Substance")**

Substance name: N-butylbenzenesulphonamide

EC number: 222-823-6

CAS number: 3622-84-2

**Decision number:** Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)

**DECISION ON A COMPLIANCE CHECK**

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of **23 February 2023**.

**A. Information required from all the Registrants subject to Annex X of REACH**

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, with the Substance, specified as follows:
  - Ten weeks pre-mating 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; and
  - Cohort 3 (Developmental immunotoxicity).

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

**Information required depends on your tonnage band**

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your

information requirements.

### **How to comply with your information requirements**

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

### **Appeal**

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to <http://echa.europa.eu/regulations/appeals> for further information.

### **Failure to comply**

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised<sup>1</sup> under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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<sup>1</sup> 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 A: Reasons to request information required under Annex X of REACH**

### **1. Extended one-generation reproductive toxicity study**

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have provided

- i) A study according to OECD TG 421 with the Substance
- ii) A reference to an earlier decision requesting an EOGRT study with the Substance<sup>2</sup>

We have assessed this information and identified the following issue(s):

- A. To be considered compliant and enable concluding if the Substance is a reproductive toxicant, the study has to meet the requirements of OECD TG 443 as specified in REACH.

With reference to i), the study you provided does not cover all relevant life stages required in OECD TG 443, as the extensive postnatal investigations of the fully exposed F1 generation up to the adulthood are not included. Furthermore, the statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 pregnant females for each test group as required OECD TG 443. In addition, there is a particular concern for developmental immunotoxicity according to column 2 of Annex X, Section 8.7.3. and information for those properties are missing.

Therefore, the study you provided does not fulfil the information requirement.

- B. In ii), you have provided a reference to an earlier decision requesting an EOGRT study on the Substance but no information that would fulfil the information requirement of Annex X, 8.7.3.

Therefore, based on the above issues A and B, an EOGRT study is required.

#### The specifications for the study design

##### *Premating exposure duration and dose-level setting*

The length of pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter pre-mating exposure duration.<sup>3</sup>

Therefore, the requested pre-mating exposure duration is ten weeks.

<sup>2</sup> <https://echa.europa.eu/documents/10162/620866a1-1217-96f5-58a0-077bf474a567>

<sup>3</sup> ECHA Guidance R.7a, Section R.7.6.2.3.2.

In order to be compliant and not to be rejected due to too low dose levels, 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. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

#### *Cohorts 1A and 1B*

Cohorts 1A and 1B belong to the basic study design and must be included.

#### *Cohort 3*

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

Existing information on the Substance itself derived from the available *in vivo* studies (OECD TG 407 and 408) show evidence of immunotoxicity:

- The OECD TG 407 study shows thymic atrophy and lymphocytolysis at non-lethal dose of 150 mg/kg bw/day.
- The OECD TG 408 study shows a decrease in absolute thymus weight in mid and high dose males and females.

Therefore, the developmental immunotoxicity Cohort 3 needs to be conducted.

#### Species and route selection

The study must be performed in rats with oral<sup>4</sup> administration.

#### *Further expansion of the study design*

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) were identified. However, you may expand the study by including the extension of Cohort 1B, and Cohorts 2A and 2B if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance<sup>5</sup>.

In your comments, submitted on behalf of the registrants, you agree with the proposed test design.

#### *Timeline*

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<sup>4</sup> ECHA Guidance R.7a, Section R.7.6.2.3.2.

<sup>5</sup> ECHA Guidance R.7a, Section R.7.6.

The timeline indicated in the draft decision to provide the information requested is 24 months from the date of adoption of the decision.

In your comments on the draft decision, you requested an extension of the timeline to 34 months. You justified your request by referring to limited test laboratory capacity, the complexity and number of steps needed for establishing a robust study design, as well as maximising the benefits of the study by taking into account all possible data, including immunotoxicity studies on the Substance which would be available at the end of 2020.

Upon ECHA's request, you provided a statement from a test laboratory which concludes that a study according to OECD TG 443 with final reporting can be completed in 21-30 months, and when a dose-range finding study is needed, the timeline would be 27-30 months.

Based on the test laboratory statement, ECHA considers that 30 months are sufficient to conduct the study and take into account the new data on immunotoxicity.

Therefore, ECHA has set the deadline to 30 months.

## **Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes**

### **A. Test methods, GLP requirements and reporting**

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries<sup>6</sup>.

### **B. Test material**

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

#### **1. Selection of the Test material(s)**

The Test Material used to generate the new data must be selected taking into account the following:

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

#### **2. Information on the Test Material needed in the updated dossier**

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers<sup>7</sup>.

<sup>6</sup> <https://echa.europa.eu/practical-guides>

<sup>7</sup> <https://echa.europa.eu/manuals>

**Appendix C: Procedure**

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

On 28 February 2017 ECHA issued decision CCH-D-2114355172-56-01/F.

On 9 September 2019 the registrant provided a 90-day sub-chronic toxicity study.

On 4 October 2019 ECHA informed the registrant that the request for an EOGRT study was withdrawn and would be addressed in this separate decision.

The compliance check of the information requirement for an extended one-generation reproductive toxicity study was initiated on 10 October 2019.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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 deadline.

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 D: List of references - ECHA Guidance<sup>8</sup> and other supporting documents**Evaluation of available information

Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping

Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)<sup>9</sup>

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)<sup>9</sup>

Physical-chemical properties

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment

Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing

Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents<sup>10</sup>

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<sup>8</sup> <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

<sup>9</sup> <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

<sup>10</sup> <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

**Appendix E: Addressees of this decision and the corresponding information requirements applicable to them**

You must provide the information requested in this decision for all REACH Annexes applicable to you.

<b>Registrant Name</b>	<b>Registration number</b>	<b>Highest REACH Annex applicable to you</b>
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.