~~Confidential~~

Helsinki, 24 November 2022

Addressees
Registrants of n-butylamine_109-73-9 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
19/07/2019

Registered substance subject to this decision ("the Substance")
Substance name: Butylamine
EC/List number: 203-699-2

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

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 ***3 March 2025***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020)

Information required from all the Registrants subject to Annex VIII of REACH

2. Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.; test method: OECD 412) by inhalation route, in rats

The reasons for the requests are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under

REACH, see Appendix 4.

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[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the decision

Contents

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

1 An in vitro gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

1.1. Information provided

2 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) *In vitro* gene mutation study in bacteria (1987) in *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 with the Substance;
(ii) *In vitro* gene mutation study in bacteria (1980) in *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 with the Substance;
(iii) *In vitro* gene mutation study in mammalian cells (2010) with the Substance;
(iv) *In vivo* micronucleus assay (1995) via oral route in mice with the Substance;
(v) *In vivo* micronucleus assay (1995) via intraperitoneal route in mice with the Substance.

3 To support your adaptation, you have also provided the following statements:

- "*No mutagenic activity of the test substance was demonstrated in any in vitro or in vivo assay in the presence or absence of metabolic activation*";
- "*n-Butylamine showed no mutagenicity in a well performed Ames test. Even though the set of test strains did not include the strain TA102 or E. Coli WP2 uvrA which can detect mutations due to formation of reactive oxygen species (ROS) or DNA cross-links, this is not regarded as a major drawback* […]. *It can reasonably be assumed that in case n-butylamine would induce ROS or DNA cross-links effects would have been detected in the other available mutagenicity tests*";
- "[…] *as neither gene mutations in mammalian cells in vitro (HPRT test) nor micronuclei in vivo (mouse micronucleus tests) were induced in these reliable genotoxicity tests, it can reasonably be assumed that n-butylamine would not have been mutagenic in the lacking tester strain in the Ames test*";
- "*Therefore, it is concluded, that on basis of this overall weight of evidence n-butylamine is not mutagenic and has not to be classified for mutagenicity*";
- "*This assessment is supported by negative findings in a OECD 471 -compliant Ames test for the structurally related n-propylamine (see corresponding IUCLID dossier) where negative results were also obtained in E.Coli WP2 uvrA.*"

4 This later statement cannot be taken into account in the assessment of your weight of evidence adaptation because the study it refers to is not an actual source of information in the form of robust study summary (eventually supported by a read-across justification).

1.2. Assessment of the information provided

5 Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

6 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory

information requirement. Subsequently, relevance, reliability, coverage, consistency, and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

1.2.1. Missing documentation of the weight of evidence

7 Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

8 You have not included a sufficient justification for your weight of evidence adaptation for the information requirement, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

9 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

1.2.2. Weight of evidence: relevance of the sources of information

10 To fulfil the information requirement, normally a study performed according to OECD TG 471 must be provided. OECD TG 471 requires the study to investigate the following key parameters: detection and quantification of gene mutation (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies.

11 The sources of information (i) and (ii) investigate the above-mentioned key parameter. Therefore, they provide relevant information that would contribute to the conclusion on this key parameter. However, the reliability of the sources of information (i) and (ii) is significantly affected as described in Section 1.2.3.

12 The sources of information (iii) to (v) do not provide relevant information on gene mutations in bacteria.

1.2.3. Weight of evidence: Significant reliability issues for sources (i) and (ii)

13 Under OECD TG 471 (2020), the following specifications must be met:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)
b) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 µl/plate.
c) At least 5 doses must be evaluated, in each test condition.
d) Triplicate plating must be used at each dose level.
e) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
f) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.
g) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

14 The sources of information (i and ii) are described as in vitro gene mutation study in bacteria. However, the following specifications are not according to the requirements of OECD TG 471 (2020):

a) The required fifth strain, i.e. *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101), in sources (i) and (ii). The plate incorporation test was only performed in one strain (TA 100) in source (ii).
b) The maximum dose tested. Although you claim in source (i) that cytotoxicity was observed at ≥ 3.333 mg/plate, the reporting does not allow an independent assessment whether the selected highest dose is justified.
c) The evaluation of at least 5 doses in each test conditions in source (ii)
d) Triplicate plating at each dose level in source (ii)
e) A positive control in source (ii)
f) A negative control in source (ii). Information whether the number of revertant colonies per plate in negative control was inside the historical control range of the laboratory in source (i).
g) Data on the number of revertant colonies per plate for the treated doses and the controls in sources (i) and (ii)

15 The reliability of sources of information (i) and (ii) is significantly affected by the deviations identified above.

16 Taken together, even if the sources of information (i) and (ii) may provide some information on the key parameter, their reliability is affected so significantly that it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 471 study.

17 On this basis, your adaptation is rejected and the information you provided does not fulfil the information requirement.

1.3. Specification of the study design

18 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable.

Reasons related to the information under Annex VIII of REACH

2. Short-term repeated dose toxicity (28 days)

19 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.).

2.1. Information provided

(i) A pre-natal developmental toxicity study via inhalation (2001) with the Substance.
(ii) A dose-finding study for a developmental toxicity study via inhalation (1999) with the Substance.

20 In your comments on the draft decision, you consider that a new 28 days repeated dose toxicity study via inhalation is not needed for the following reasons:

- *"After inhalation exposure no systemic toxic dose can be reached which might cause adverse systemic effects, as the inhalation exposure concentration is limited due to the local irritating properties of n-butylamine."*
- *"based on the observations in the developmental toxicity study with inhalation exposure even lower concentrations should be applied in a 28 day inhalation study for ethical reasons, for which it could be plausibly assumed that they will not provide cause systemic effects."*
- *"A 28 day study with n-butylamine would therefore not provide any additional information on possible systemic effects after repeated dose exposure and should for animal-welfare reasons not be performed."*

21 Furthermore, in your comments on the draft decision, you refer also to the following studies on analogue substances to support your justification that 28 days study via inhalation is not needed:

(iii) A pre-natal developmental toxicity study via oral route (2002) with an analogue substance Butylammonium chloride (EC No 223-369-1).
(iv) A sub-chronic repeated dose toxicity study via inhalation (1996) with an analogue substance n-butyl acetate.

2.2. Assessment of information provided

2.2.1. Studies (i) to (ii) do not comply with the applicable test guideline

22 (Eco)toxicological studies must comply with a recognised test method (Art. 13(3) of REACH), in this case OECD TG 412. Such study must cover the key parameters of the corresponding OECD test guideline (Art. 13(3) of REACH). Therefore, the following specifications must be met:

a) an exposure duration of at least 28 days;
b) at least 5 male and 5 female animals for each concentration and control group;
c) functional observations;
d) haematology and clinical biochemistry;
e) gross necropsy and histopathology of the organs listed in the OECD TG 412 at the end of the study.

23 The studies (i) and (ii) are described as "Short-term repeated dose toxicity studies". The study (i) has been conducted using OECD TG 414 which investigates pre-natal developmental toxicity rather than repeated dose toxicity. The study (ii) is a dose-finding study for a developmental toxicity study and claimed to be similar to OECD TG 412. In any

case, the studies (i) and (ii) do not cover the key specifications of the OECD TG 412 such as:

a) an exposure duration of at least 28 days as the treatment lasted only 14 days (i) or 5 days (ii);
b) testing of both sexes as only females rats were used in the studies (i) and (ii);
c) functional observations in the studies (i) and (ii);
d) haematology and clinical biochemistry in the study (i);
e) gross necropsy and histopathology of the organs listed in the OECD TG 412 at the end of the study in the studies (i) and (ii).

24 Therefore, the studies do not comply with the specifications of the applicable test guideline.

2.2.2. Your justification to omit the study provided in your comments to the draft decision has no legal basis

25 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex VIII, Section 8.6.1., column 2.

26 In your comments on the draft decision, you consider that 28 days study is not needed as it would not provide any additional information on possible systemic toxicity after repeated dose exposure. In a pre-natal developmental toxicity study, local irritation in respiratory tract was observed with all concentrations tested but no systemic toxicity at any tested concentrations. Furthermore, in your comments on the draft decision, you refer to a pre-natal developmental toxicity study via oral route (iii) and a sub-chronic toxicity study via inhalation route (iv) on analogue substances. With regard the information from studies (iii) and (iv), ECHA understands that you do not aim to apply read-across adaptations under Annex XI, Section 1.5. to fulfil the information requirement. ECHA also understands that you only provided this information to support your presumption that, after inhalation exposure, no adverse systemic effects are to be expected as the inhalation exposure concentration is limited due to the local irritating properties of the Substance.

27 The Substance has a harmonised classification as Skin Corr. 1 A (H314). Furthermore, in the introduction to Annex VIII to REACH, it is stated "*In vivo testing with corrosive substances at concentrations/dose level causing corrosivity shall be avoided*". However, ECHA notes that corrosivity/irritation is not an adaptation possibility as such.

28 On this basis, ECHA concludes that this justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex VIII, Section 8.6.1., column 2.

29 Moreover, irrespective of the above, ECHA notes that the supporting information from similar substances provided as part of your comments (studies (iii) and (iv)) would not provide a reliable basis for a read-across adaptation:

- First, you have not provided any read-across justification for the prediction.
- For study (iii), ECHA acknowledges that read-across from butylammonium chloride may be plausible as such for the prediction of systemic effects as the source substance is a neutralised salt of the Substance. However, as already explained under Section 2.2.1., a PNDT study does not provide an adequate coverage of the key specifications of an OECD TG 412. In pre-natal developmental toxicity studies (OECD TG 414), a more limited number of examinations on systemic toxicity is performed compared to a 28 days repeated dose toxicity study (OECD TG 412). Therefore, it is not possible to completely exclude the possibility that some adverse systemic effects could be observed in a 28 days study via inhalation already at the concentration levels which can be tested despite corrosivity/irritation.
- For study (iv), in the absence of a robust study summary, ECHA cannot assess the validity of this information.

30 Therefore, you have not demonstrated that this information can be omitted.

31 Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI or Annex VIII, Section 8.6.1., column 2.

32 Based on the above, the information you provided do not fulfil the information requirement.

2.3. Specification of the study design

33 Following the criteria provided in Annex VIII, Section 8.6.1, Column 2, the inhalation route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance; Guidance on IRs and CSA, Section R.7.5.6.3.1. because the Substance is a liquid of very high vapour pressure (>10 kPa at 20 °C) and human exposure by the inhalation route is reported in the registration.

34 In your comments on the draft decision, you agree that the most appropriate route of exposure for testing repeated dose toxicity of the Substance is inhalation.

35 According to the OECD TG 412, the rat is the preferred species.

36 Therefore, the study must be performed according to the OECD TG 412, in rats and with administration of the Substance by inhalation.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

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

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

The compliance check was initiated on 06 July 2021.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the requests by removing the request for Short-term testing on fish according to OECD TG 203. Other requests were not amended.

The deadline of the decision is set based on standard practices for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[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.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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[2].

1.2. 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[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals