EUROPEAN CHEMICALS AGENCY

Helsinki, 11 March 2020

Addressees
Registrants of [redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
19 November 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: N-tert-butylacrylamide
EC number: 203-505-6
CAS number: 107-58-4

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

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by ***19 December 2022***.

A. Requirements applicable to 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 EU B.13/14. / OECD TG 471) with the Substance;

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method EU C.2./OECD TG 202) with the Substance;

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. Only if a negative result in *in vitro* gene mutation study in bacteria Annex VII, Section 8.4.1 is obtained, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance;

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance;

3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method OECD TG 203) with the Substance;

C. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats with the Substance;

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD

TG 414) in a first species (rat or rabbit), oral route with the Substance;

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method EU C.20./OECD TG 211) with the Substance;

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses common arguments that are applicable throughout the present decision while the other Appendices state further the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The test material used to perform the required studies must be selected and reported in accordance with the specifications prescribed in the Appendix entitled Observations and technical guidance.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of 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 on general considerations

The ECHA Guidance documents are listed in the Appendix entitled Observations and technical guidance.

(i) Assessment of the weight-of-evidence adaptations, under Annex XI, Section 1.2.

In your registration dossier, you have adapted the following standard information by applying a weight of evidence (WoE) approach in accordance with Annex XI, Section 1.2:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

In your registration dossier, you provide information on:

- the Substance
- analogue substances:
  - N-(1,1,3,3-tetramethylbutyl) acrylamide / EC 224-169-7 / CAS 4223-03-4;
  - N,N'-Methylenebisacrylamide / EC 203-750-9 / CAS 110-26-9;
  - acrylamide / EC 201-173-7 / CAS 79-06-1.

We have assessed this information and identified the following general issues:

For adaptations using the WoE according to Annex XI, Section 1.2., it should be demonstrated that there is sufficient WoE from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property with respect to the information requirement in question while the information from each single source alone is regarded insufficient to support this notion.

Whenever sources of information derived from analogue substances are used as part of the WoE (in this case, screening for reproductive/developmental toxicity and pre-natal developmental toxicity), the characterisation of the analogue substances identified needs to be as detailed as possible, the results of the studies must have adequate and reliable coverage of the key parameters and a reasoning needs to be provided to establish why information from analogue substances can reliably be read-across.

You have provided endpoint summaries for repeated dose toxicity, developmental toxicity and toxicity to reproduction.

However, whilst the submitted reports can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance and relialibity of the individual sources of information. No assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.

Regarding the information on analogue substances, you neither provided detailed information on the identity of the source substances, in particular the composition of the test materials, nor reasoning establishing why information from analogue substances can reliably contribute to the WoE adaptation to conclude on the presence or absence of the particular dangerous property of the Substance. In the absence of this information ECHA cannot contribute any weight to this information in its assessment of the compliance of your adaptation based on WoE.

As your weight of evidence adaptations are not supported by adequate documentation for the reasons presented above, they do not comply with the general rules of adaptation as set out in Annex XI, Section 1.2 and are rejected by ECHA.

In addition to the above endpoints, in your comments to the draft decision you propose to adapt the following standard information requirements by applying weight of evidence (WoE) approach in accordance with Annex XI, Section 1.2:

- Short-term toxicity on aquatic invertebrates (Annex VII, Section 9.1.1.);
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.); and
- Short-term toxicity on fish (Annex VIII, Section 9.1.3.).

In your comments to the draft decision, you additionally refer to further information on the following substances:

- acrylamide [CAS: 79-06-1; EC: 201-173-7],
- N,N'-methylenediacrylamide [CAS: 110-26-9 ;EC: 203-750-9],
- t-butyl alcohol [CAS: 75-65-0; EC: 200-889-7].

However, even when considering the additional information, ECHA consider that for the following general reasons the adaptation cannot be accepted:

1. Relevance of information – requirement for a scientific justification for the use of information from similar substances

Based on the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

You have attached a document to your comments to the draft decision intended to justify the use of information obtained on the aforementioned similar substances in your WoE adaptation. This document presents a set of physico-chemical properties and alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of these similar substances. On the basis of this information you derive conclusions on the structural similarities, similarities in physico-chemical properties and similarities in the alert profiles between the Substance and each of the above similar substance. You conclude that "*Based on structural similarity, reactivity, physical–chemical properties, and general mechanistic approach, the above were identified as read-across materials with sufficient data for toxicological evaluation*".

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data[2]. However, you did not provide information on the applicability domain of the expert systems to generate the alert profiles. Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as growth inhibition on aquatic plants, short term toxicity to aquatic invertebrates and fish and reproductive toxicity, QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints. You have not provided robust scientific information, including relevant and reliable studies of comparable design and duration, establishing why the (eco)toxicological properties of the Substance can be determined from information on the similar substance. In the absence of information ECHA cannot contribute any weight to this information in its assessment of the compliance of your

[2] ECHA Guidance R.4, Section R.4.3.2.2.

adaptation based on WoE.

2. Reliability of the information on similar substances

- Information obtained from the QSAR Toolbox in your comments to the draft decision

The ECHA Guidance R.4, Section R.4.2 informs on the criteria for assessing the reliability of information provided as part of WoE adaptations. The availability of raw data from the studies and an adequate description of the studies are listed among the key elements to be assessed to determine if and how the information can be used in the adaptation. This ECHA Guidance indicates that "*where critical supporting information is not reported (e.g. species tested, substance identity and dose procedure) the test data should be considered to be unreliable for the purposes of REACH*".

Your WoE adaptations are partly based on information on similar substances obtained through the use of data from the QSAR Toolbox. The QSAR Toolbox prediction reports provided to support the use of this data do not include any information on the test procedures applied, and on the results of the studies on the similar substances. In the absence of this information, the information from the QSAR toolbox referred to in your WoE adaptations is considered unreliable.

- Information on analogue substances referred to in your comments

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified studies conducted with analogue substances that you intend to use as sources of information in your weight of evidence approach and provided high-level narratives presenting these studies.

You have not provided robust study summaries for any for these source studies. In particular you have not provided detailed information on the methods, results and conclusions of these studies allowing for an independent assessment of the studies. In the absence of such information, we cannot assess the reliability of the information from these studies.

3. Requirement for documentation of the WoE adaptations

ECHA Guidance R.4.4 specifies that a WoE adaptation must involve an assessment of the relative values / weights of the several pieces of available information. This assessment must consider for instance the relevance and reliability of the information, the consistency of results/data, the nature and severity of effects. The lines of evidence should be integrated considering their relative values or weights in order to draw a conclusion. The assessment should be documented and included in your technical dossier.

You have provided WoE summaries in the endpoint summaries for repeated dose toxicity, developmental toxicity, toxicity to reproduction, growth inhibition on aquatic plants, short term toxicity to aquatic invertebrates and fish and reproductive toxicity. In this summary you briefly present each of the sources of information, specify the dose descriptors obtained from these studies and outline the effects observed/the absence of effects observed in these sets of data. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these reports can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance, reliabilty of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations. Therefore your weight-of-evidence adaptation is not supported by adequate documentation.

4. Conclusion of the WoE assessment

As in your WoE adaptations a documented scientific justification for the relevance and reliability of the provided data on the similar substances, which would allow reaching a conclusion on the relevant hazard properties of the Substance, is missing, they do not comply with the general rules of adaptation as set out in Annex XI, Section 1.2. Therefore, your adaptations are rejected.

(ii) Assessment of the QSAR adaptations, under Annex XI, Section 1.3.

You have adapted the following standard information requirements by applying QSAR approach in accordance with Annex XI, Section 1.3:

- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

We have assessed this information and identified the following general issue:

For the use of QSAR models under Annex XI, Section 1.3., the following cumulative conditions must be met: results are derived from a (Q)SAR model whose scientific validity has been established, the substance falls within the applicability domain of the model, results are adequate for the purpose of classification and labelling and/or risk assessment, and adequate and reliable documentation of the applied method is provided.

In order to verify the scientific validity of the model, whether the Substance falls within the applicability domain of the model, and ultimately whether the prediction is adequate for the purposes of classification and labelling, ECHA requires a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF), as set out in ECHA's Practical guide "How to use and report (Q)SARs"[3], section 3.4.

However, you have not provided any documentation for the QSAR prediction. In particular, you have not included a QMRF or a QPRF in your technical dossier.

As explained above, ECHA cannot establish whether the model is scientifically valid, whether the Substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment. Your adaptations according to Annex XI, section 1.3 are therefore rejected.

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

Appendix A: Reasons for the requests to comply with Annex VII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to the REACH 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 in Annex VII to REACH.

You have provided a key study in your dossier: Bacterial reverse mutation assay (Hashimoto and Tanii, 1985) with the following strains, S. typhimurium TA 1535, TA 1537, TA 1538, TA 100 and TA 98, which all gave negative results.

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

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997). The key parameter(s) of this test guideline include that 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).

However, the reported data in the study did not include the appropriate 5 strains, as the information provided does not include results in the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). Therefore, the information provided does not cover key parameters required by OECD TG 471.

In your comments to the draft decision you agree to provide the information for the missing 5th strain. Regarding ECHA's assessment you still

a) state that the key study (Hashimoto and Tanii, 1985) together with results from "Danish QSAR" fulfil the information requirement,
b) question the need to perform the mutagenicity test with 5 bacterial strains by referring to paragraph 13 of the OECD TG 471 (1997), and state that "*The guideline however does not mention that the testing should be a combination of these strains.*" and "[the guideline] *does not mandate to include TA102 or add a DNA repair-proficient strain of* E.coli."
c) refer to a study (Bonneau et al., 1991) to justify that the strain TA1538 could be regarded as a potential substitution to strain TA102 in an Ames test.

We have assessed this additional information and identified the following issues:

a) ECHA understands that by "Danish QSAR" you refer to the mechanistic triggers and structural alerts provided in your read-across justification document. As explained under General considerations, section (i).2. your read-across adaptation is rejected.
b) ECHA does not agree with your understanding of paragraph 13 of OECD TG 471 adopted in 1997. This paragraph makes four clear statements ("*At least five strains of bacteria should be used; These should include four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100); 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 (19) which have an AT base pair at the primary reversion site*") before making a clear conclusion: "*Therefore the recommended combination of strains is:*

- *1. S. typhimurium TA1535, and*
- *2. S. typhimurium TA1537 or TA97 or TA97a, and*
- *3. S. typhimurium TA98, and*
- *4. S. typhimurium TA100, and*
- *5. E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102".*

ECHA's understanding of paragraph 13 of the OECD TG 471 (1997) is in agreement with all experienced and accredited CROs have been performing the Ames test since the OECD TG 471 was updated in 1997. This common understanding is that the aforementioned strains must be tested when performing the Ames test.
Moreover, the wording of the OECD TG 471 was updated from "*At least four strains, TA 1535, TA 1537, TA 98 and TA 100 should be used* [version 1983]" to "*At least five strains of bacteria should be used* [version 1997]". Moreover, the 1997 clearly described the nature of the 5th strain. This 5th strain is now a key feature of the current OECD TG 471.

c) Strains TA1538 and TA102 detect two different types of mutations (frameshift vs. base pair substitution, respectively). The article of Bonneau et al. (1991) was available when the OECD working group updated the OECD TG 471 (which was adopted in 1997), but this working group came to a different conclusion than the paper of Bonneau et al. The OECD TG 471 adopted in 1997 (which is still in application today) was agreed by all countries that contribute to the OECD activities and ensure the application of the mutual acceptance of data across the world.

Therefore, the information requirement is not fulfilled.

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

You have provided a key study "Determination of the inhibition of the mobility of daphnids" ([redacted] 2018).

According to Article 13(4) of REACH, ecotoxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

The study you provided was conducted according to OECD TG 202 but it was not performed in compliance with GLP.

In your comments to the draft decision you confirm that the key study with the Substance was conducted in a laboratory that is not GLP accredited.

Furthermore, in your comments to the draft decision you have referred to following additonal information:

- A study on proposed analogue substance t-butyl alcohol (EC 200-889-7) obtained through the use of data from the QSAR Toolbox and you say that "*All the study protocol was followed as mentioned in the OECD 202*", and
- A study on proposed analogue substance 2-methyl-2-propenamide (EC 201-202-3) obtained through the use of data from the QSAR Toolbox and you say that the study was "*following the guidelines similar to OECD 202*".

We understand that you intend to use this information alongside the information from study on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2.

However, we have assessed this information and for the reasons given in the Appendix on General considerations above reject the proposed adaptation. As explained in more detail in that Appendix, the information obtained from QSAR Toolbox and information on the similar substances provided in your comments is not considered reliable and relevant for the purpose of identification of the hazard of the Substance. Your WoE adaptation is also not supported by adequate documentation.

Therefore, the information requirement is not fulfilled.

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided a key study "Freshwater algal growth inhibition test" ([redacted] 2018) and a supporting study "Aquatic Toxicity Study of N-tert-butylacrylamide (CAS No. 107-58-4) on Chlorella vulgaris in a Static System" ([redacted] 2014).

According to Article 13(4) of REACH, ecotoxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

Both studies you provided were conducted according to OECD TG 201 but they were not performed in compliance with GLP.

In your comments to the draft decision you confirm that the key study with the Substance was conducted in a laboratory that is not GLP accredited.

Furthermore, in your comments to the draft decision you have referred to the following information:

- A study on proposed analogue substance 2-methyl-2-propenamide [CAS: 79-39-0; EC Number: 201-202-3] obtained through the use of data from the QSAR Toolbox and you say that the study was "*following the guidelines similar to OECD 201*", and
- An OECD TG 201 study (from "*peer reviewed journal*")on proposed analogue substance t-butyl alcohol [CAS: 75-65-0; EC Number: 200-889-7].

We understand that you intend to use this information alongside the information from study on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2.

However, we have assessed this information and for the reasons given in the Appendix on General considerations above reject the proposed adaptation. As explained in more detail in that Appendix, the information obtained from QSAR Toolbox and information on the similar substances provided in your comments is not considered reliable and relevant for the purpose of identification of the hazard of the Substance. Your WoE adaptation is also not supported by adequate documentation.

Therefore, the information requirement is not fulfilled.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to the REACH Regulation.

1. **Only if a negative result in *in vitro* gene mutation study in bacteria Annex VII, Section 8.4.1 is obtained (study requested under section A.1) , In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)**

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

Your dossier contains data for an *in vitro* gene mutation study in bacteria, and data for an *in vitro* cytogenicity study in mammalian cells. The information for *in vitro* gene mutation study in bacteria is rejected for the reasons provided in sections A.1.

The result of the request for information in sections A.1 will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

You have provided a key study in your dossier: *In vitro* gene mutation study in mammalian cells, with and without metabolic activation (according to OECD TG 476, GLP compliant, 2015).

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

To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490. The key parameter(s) of these test guidelines include:

a) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
b) The response for the concurrent negative control must be inside the historical control range of the laboratory.
c) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

However, the reported data for the study you have provided do not include:

a) one positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control
b) A negative control with a response inside the historical control range of the laboratory.
c) The reporting of data on cytotoxicity and of mutation frequency for the treated and control cultures.

In your comments to the draft decision you

a) indicated that the provided study did include a positive and a negative control. You, however, admitted that the study did not report data on statistically significant increase of the positive control, and data on negative control regarding the historical range of the laboratory. You state that the requirement for the positive control to procude a statistically significant increase was not included in the guideline version before 2015,
b) submitted a brief summary of the following new studies with analogue substances:

i. Mouse lymphoma assay ([redacted] 1995), proposed analogue substance t-butyl alcohol [CAS: 75-65-0; EC: 200-889-7], no guideline, no GLP, no RSS, and
ii. Mouse lymphoma assay ([redacted] 2005), proposed analogue substance N-(1,1,3,3-tetramethylbutyl)acrylamide [CAS: 4223-03-4; EC Number: 224-169-7], OECD TG 476, no GLP, no RSS.

We have assessed your comments and identified the following issues:

a) ECHA points out that the requirement for the positive control was included in the OECD TG 476 version of 1997 (last version before the introduction of the current 2016 version).
b) We understand that you intend to use the information from studies (i) and (ii) alongside the information from study on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2. However, as explained under General considerations above, your adaptation is rejected.

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

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria provides a negative result.

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

A Screening for reproductive/developmental toxicity study (OECD TG 421 or 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have adapted this information requirement by using a weight of evidence approach under Annex XI, Section 1.2. of REACH. In support of your adaptation of this information requirement, you have provided the following information for this endpoint in your dossier:

With the Substance:

(i) Screening for reproductive/developmental toxicity, male mice. 10 weeks. (No guideline followed, GLP not specified. Hashimoto et al 1981) One dose 317.975 mg/kg bw.
(ii) Short-term (28-day) repeated dose toxicity study in female rats, via oral-gavage (according to OECD TG 407, GLP[redacted] 2014). Doses: 0, 125, 250, 500 mg/kg bw/day. 5 animals/sex/dose.

With the analogue substance N-(1,1,3,3-tetramethylbutyl) acrylamide/ EC: 224-169-7 / CAS: 4223-03-4:

(iii) Combined Repeated, Reproductive and Developmental Toxicity Screening Test, Rats, (no guideline, non GLP compliant; assigned reliability of 4; J Rhodes. 2004), 0, 70, 155, 350 mg/kg bw/day/ 10 animals/sex/dose. NOAEL 350 mg/kg bw/day) (male/female).

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

As explained in the Appendix on General considerations, ECHA rejects the adaptation already

due to the lack of adequate documentation.

Furthermore, the robust study summaries must cover critical information for conclusions on effects of the Substance on male and female reproductive performance as well as specific target organ toxicity as referred in OECD TG 421/422, among others:

- Dosing of the Substance for a minimum of four weeks for males and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation,
- Examination of key parameters for toxicity such as clinical signs/body weight/body weight changes/food consumption/thyroid hormone assessment (P0 and F1), and
- Monitoring of oestrus cycles.

However, neither study (i) nor study (ii) provide this critical information, because the 28-day short-term study and the 10 weeks repeated dose toxicity study in male mice do not

- have the required exposure duration, i.e. it do not cover the relevant life stages (two weeks of premating and pregnancy and at least 13 days of lactation),
- cover key parameters of reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition, and
- monitor the oestrus cycles.

For study (iii), ECHA agrees with your assessment that the study is not reliable according to the Klimisch Score assigned by you (KL4). The documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

In conclusion, you have neither adequately explained how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property as investigated in a Screening for reproductive/developmental toxicity according to OECD TG 421/422 study nor is the provided information reliable or relevant in this regard.

Therefore, the integration of the information provided by the aforementioned studies do not provide adequate and reliable coverage of the key parameters.

In your comments to the draft decision you

a) describe the adaptation already addressed in the draft decision notified to you, and
b) submit a new read-across justification but with the same source study performed on the proposed analogue substance N-(1,1,3,3-tetramethylbutyl) acrylamide (EC 224-169-7).

We have assessed this information and identified the following deficiencies:

a) you have not addressed the deficiencies in the studies mentioned in our assessment above, and
b) as explained under General considerations above, your adaptation is rejected.

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

Information on study design

A study according to the test method OECD TG 421/422 should be performed in rats with oral[4] administration of the Substance.

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH.

You have provided a key study "Aquatic Toxicity Study of N-tert-butylacrylamide (CAS No. 107-58-4) on Zebra Fish ([redacted]) in a Static System" (2013).

According to Article 13(4) of REACH, ecotoxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

The study you provided was conducted according to OECD TG 203 but it was not performed in compliance with GLP.

In your comments to the draft decision you confirm that the key study with the Substance was conducted in the laboratory that is not GLP accredited.

Furthermore, in your comments to the draft decision you have referred to the following information:

- A non-guideline study on proposed analogue substance N, N'-methylenediacrylamide (CAS: 110-26-9; EC number: 203-750-9) obtained through the use of data from the QSAR Toolbox, and
- An OECD TG 203 study on proposed analogue substance t-butyl alcohol (CAS: 75-65-0; EC Number: 200-889-7) obtained through the use of data from the QSAR Toolbox.

We understand that you intend to use this information alongside the information from study on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2.

However, we have assessed this information and for the reasons given in the Appendix on General considerations above reject the proposed adaptation. As explained in more detail in that Appendix, the information obtained from QSAR Toolbox and information on the similar substances provided in your comments is not considered reliable and relevant for the purpose of identification of the hazard of the Substance. Your WoE adaptation is also not supported by adequate documentation.

Therefore, the information requirement is not fulfilled.

[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix C: Reasons for the requirements applicable to all the Registrants subject to Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to the REACH Regulation.

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

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have adapted this information requirement by using a weight of evidence approach under Annex XI, Section 1.2.

You have provided 3 studies for this endpoint in your dossier:

i. Short-term (28-day) repeated dose toxicity study in female rats, via oral-gavage (according to OECD TG 407, GLP, [redacted], 2014).
ii. Repeated dose oral toxicity study (10-weeks) (Tanii and Hashimoto, 1983. Publication) in mice. No guideline followed, GLP not specified. One dose 317.975 mg/kg bw.
iii. Repeated dose oral toxicity study (90d) (Tanii and Hashimoto, 1983. Publication) in rats. No guideline followed, GLP not specified. One dose 1907.85 mg/kg bw.

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

As explained in the Appendix on general considerations, ECHA rejects the adaptation already due to the lack of adequate documentation.

Furthermore, the robust study summaries must cover critical information for conclusions as in a subchronic toxicity study conducted accoring to OECD TG 408, which includes:

- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study, and
- at least 10 female and 10 male animals should be used at each dose level (including control group).

However, the study (i) you have provided does not fulfil the above criteria because the 28-day short-term studies

- do not have the required exposure duration of 90 days,
- were conducted with less than 10 animals per sex per test dose group. Thus the statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408.

For studies (ii) and (iii), the robust study summary submitted in your technical dossier does neither contain the information on the technical guideline followed, if any, nor the GLP compliance of the study, nor a clear description of the identity and composition of the test material. It does also not provide any observations on the use of at least three dose levels and a concurrent control and of at least 10 female and 10 male animals that should be used at each dose level (including control group), clinical observations, ophthalmological examination, clinical biochemistry, and pathology of sexual (male and female) organs, full detailed gross necropsy and subsequent histopathology of both types tissues. Therefore the documentation of these studies does not allow ECHA to conduct an independent assessment. It cannot attribute any weight to these studies.

In conclusion, you have neither adequately explained how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property as investigated in a Subchronic toxicity study nor is the provided information reliable or relevant in this regard.

In your comments to the draft decision you describe the above mentioned studies. You also state that the two studies by Tanii and Hashimoto (1983) and Hashimoto (1981) "*were inconclusive to meet the data requirements of Annex IX registration*" of your Substance, and "*the studies provided in the dossier have satisfied the data requirements of Annex IX*". Finally, you state that "*If ECHA insists then we may ready to consider to conduct the OECD 408 study to further confirm the data requirements and classification of the substance.*"

We have assessed this information and conclude that you have not addressed the shortcomings identified above, i.e. with regard to the required exposure duration of 90 days and the required number of tested animals as they are set in OECD TG 408. You also seem to agree to perform the requested study.

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

Information on the study design

The sub-chronic toxicity study must be performed by the oral route according to the OECD TG 408, in rats, because although the information indicate that human exposure to the Substance by the inhalation route is likely, potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation, local effects.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement in Annex IX to REACH.

You have adapted this information requirement by using a weight of evidence approach under Annex XI, Section 1.2. by providing study records with analogue substances:

with N,N'-Methylenebisacrylamide / EC 203-750-9 / CAS 110-26-9:

(i) Prenatal Developmental Toxicity Study in mice (gavage), OECD Guideline 414 (1992), No GLP compliance

with N-(1,1,3,3-tetramethylbutyl) acrylamide / EC 224-169-7 / CAS 4223-03-4:

(ii) Combined Repeated, Reproductive and Developmental Toxicity Screening Test in Rats Crl:WI(Glx/BRL/Han)BR, (2004), No GLP compliance.

with acrylamide / EC 201-173-7 / CAS 79-06-1:

(iii) Developmental toxicity study in rats, GLP compliance not specified, (1988).

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

As explained in the Appendix on General considerations, ECHA rejects the adaptation already due to the lack of adequate documentation.

Furthermore, the robust study summaries would have to cover critical information for conclusions on pre-natal developmental toxicity study, among other elements:

- examination of the dams for weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight and uterine content;
- examination of the sex ratio, external, skeletal and soft tissue alterations (variations and malformations), number of resorptions and or live foetuses, measurement of anogenital distance in live rodent foetuses.

However, none of the studies you have reported provide adequate coverage of these key parameters. More specifically, neither study (i) nor study (ii) meet the above criteria, because:

- the weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight and uterine content have not been examined in the dams, and
- the sex ratio, the external, skeletal and soft tissue alterations (variations and malformations), number of resorptions and or live foetuses, measurement of anogenital distance in live rodent foetuses have not been examined.

ECHA further agrees with your assessment that study (ii) has to be disregarded in the assessment (Klimisch score 4). It is not GLP compliant and the documentation provided does not allow to assess its reliability.

In conclusion, you have neither adequately explained how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property as investigated in a Pre-natal developmental toxicity study nor is the provided information reliable or relevant in this regard.

In your comments to the draft decision, you state that "*We will consider this request from ECHA and get the testing done for OECD TG 414 (Pre-Natal Developmental toxicity test) guideline to support the classification of the substance.*"

ECHA understands that you agree to perform the requested study.

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

Information on the study design

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[4] administration of the Substance.

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Long-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex IX to the REACH Regulation.

You have adapted the standard information requirement by using a Qualitative or Quantitative structure-activity relationship ((Q)SAR) under Annex XI, Section 1.3. Your adaptation is based on the following study record in your dossier:

- QSAR calculation "Long-term toxicity to aquatic invertebrates by ECOSAR Version 1.11" using the Substance (key study, reliability score 2, 2018).

However, for the reasons explained in the Appendix on general considerations regarding the assessment of the QSAR adaptations (ii), your adaptation is rejected.

In your comments on the draft decision you

a) claimed that you have attached a QMRF report for the prediction rejected in the draft decision notified to you; and

b) stated that *"as per the chemical safety assessment, all the risk related to environmental risk characterization are controlled with the available data. Thus no further testing is needed since all risks are controlled as per annex I section 3 of the REACH regulation"*.

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

a) no QMRF and/or QPRF was attached to the comments on the draft decision or in the technical dossier. Therefore, the information in your comments does not address the concerns identified in the draft decision.

b) We understand that you intend to adapt this standard information requirement according to Annex IX, Section 9.1., Column 2 of REACH.

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity study on aquatic invertebrates must be performed unless the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the use of the Substance are controlled (Annex I, section 0.1). The justification must be documented in the Chemical Safety Assessment.

In particular, the Chemical Safety Assessment must take into account the following elements to support that long-term toxicity testing is not required:

- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

In your comments on the draft decision, you did not submit any specific justification as to why the risks of the Substance are controlled.

As specified in requests A.2-A.3, B.3 and C.3-C.4 of this decision, the data on aquatic toxicity is not compliant. Hence your dossier currently does not include adequate information to characterize the hazard property of the Substance. Without this information your Chemical Safety Assessment does not demonstrate that the risks are adequately controlled and that the Substance is correctly classified for environmental hazards. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1., Column 2.

Based on the above, the information requirement is not fulfilled.

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Long-term toxicity testing on fish is a standard information requirement in Annex IX to the REACH Regulation.

You have adapted the standard information requirement by using a Qualitative or Quantitative structure-activity relationship ((Q)SAR) under Annex XI, Section 1.3. Your adaptation is based on the following study record in your dossier:

- QSAR calculation "Long-term toxicity to fish" using the ECOSAR Version 1.11 for the Substance (key study, reliability score 2, 2017).

However, for the reasons explained in the Appendix on general considerations regarding the assessment of the QSAR adaptations (ii), your adaptation is rejected.

In your comments on the draft decision you

a) claimed that you have attached a QMRF report for the prediction rejected in the draft decision notified to you; and

b) stated that "*as per the chemical safety assessment, all the risk related to environmental risk characterization are controlled with the available data. Thus no further testing is needed since all risks are controlled as per annex I section 3 of the REACH regulation*".

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

a) no QMRF and/or QPRF was attached to the comments on the draft decision or in the technical dossier. Therefore, the information in your comments does not address the concerns identified in the draft decision.

b) We understand that you intend to adapt this standard information requirement according to Annex IX, Section 9.1., Column 2 of REACH.

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity study on fish must be performed unless the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, Section 0.1). The justification must be documented in the Chemical Safety Assessment.

In particular, the Chemical Safety Assessment must take into account the following elements to support that long-term toxicity testing is not required:

- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

In your comments on the draft decision, you did not submit any specific justification as to why the risks of the Substance are controlled.

As specified in requests A.2-A.3, B.3 and C.3-C.4 of this decision, the data on aquatic toxicity is not compliant. Hence your dossier currently does not include adequate information to characterize the hazard property of the Substance. Without this information your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled and that the Substance is correctly

classified for environmental hazards. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1., Column 2.

Based on the above, the information requirement is not fulfilled.

Appendix D: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 5 February 2019.

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 did not amend the request(s).

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 E: Observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   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: 'How to report robust study summaries[5]'.

4. Testing strategy for aquatic toxicity testing

   Before conducting the requested aquatic toxicity tests (requests A.2, A.3, B.3, C.3, C.4) you should consult the Integrated Testing Strategy described in ECHA Guidance R.7b, Section R.7.8.5 (including Figure R.7.8-4), on the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct all the requested studies, in particular the long-term fish toxicity study. Furthermore, REACH Annex VII Section 9.1.1 and Annex VIII Section 9.1.3 describe that you may consider conducting the long-term toxicity testing on daphnia and fish (C.3, C.4) directly instead of short-term testing (A.2, B.3).

   If you decide to omit some of the studies requested in this decision, you must provide full documentation to justify the adaptation.

5. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example,

[5] https://echa.europa.eu/practical-guides

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.

Technical reporting of the test material

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[6].

6. List of references of the ECHA Guidance documents[7]

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 in this decision.

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[8]

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

[6] https://echa.europa.eu/manuals
[7] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[8] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

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.

Appendix F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]