~~Confidential~~

Helsinki, 26 April 2022

Addressees
Registrant(s) listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
03/04/2020

Registered substance subject to this decision ("the Substance")
Substance name: 3-methyl-1,3-butandiol
EC number: 459-270-7

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 May 2023***.

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

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

The reasons for the decision(s) 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

0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. Predictions for toxicological properties

5 You provide a read-across justification document in IUCLID Section 13.

6 You predict the properties of the Substance from information obtained from the following source substance:

1,3-butanediol, EC 203-529-7

7 You provide the following reasoning for the prediction of toxicological properties: ”Read-across from 1,3-butylene glycol to 3-methyl-1,3-butanediol regarding the endpoints in vitro gene mutation study in mammalian cells and reproductive toxicity – screening study for reproductive/developmental toxicity is justified by the data comparison of the structural and physic-chemical similarity, similar toxicity profiles and similar environmental fate and environmental toxicity”.

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

9 We have identified the following issue(s) with the prediction(s) of toxicological properties:

0.1.1.1. Missing supporting information

10 Annex XI, Section 1.5 of the REACH Regulation states that “physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)”. For this purpose “it is important to provide supporting information to strengthen the rationale for the read-across” (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

11 Supporting information must include bridging studies to compare properties of the Substance and source substances.

12 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

13 Regarding the requirement for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.), no study with the Substance is available in the registration dossier. You only provided information on the following in vivo studies with the source substance, extracted from a publication (1981):

- a non-guideline Rodent dominant lethal test in rats
- a non guideline in vivo cytogenetic study over three generations in rats.

14 Regarding the requirement for a reproductive/developmental toxicity screening study (Annex VIII, Section 8.7.1.), no study with the Substance is available in the registration dossier. You only provided information on the following study with the source substance, extracted from a publication (1981):

- a non-guideline five-generation reproduction study in rats.

15 Without bridging studies of comparable design and duration for the Substance and of the source substance for each endpoint, it is not possible to compare their properties and confirm that both substances cause the same type of effects.

16 In addition, specific reasons why the above source studies cannot be considered reliable are explained further below under the relevant information requirement sections 1 and 2. Therefore, the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and of the source substance to support your read-across hypothesis.

17 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

0.1.1.2. Adequacy and reliability of source studies

18 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

(1) have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

19 Specific reasons why the studies on the source substance do not meet these criteria are explained further below under the applicable information requirement sections 1 and 2. Therefore, no reliable predictions can be made for these information requirements.

0.1.2. Conclusion on the read-across approach

20 For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s).

21 In the comments to the draft decision, you acknowledge the above deficiencies and you indicate your intention to improve the read-across approach using new source substances,

but you have not provided any further information. Without this information, no conclusion on the compliance of the proposed adaptation can be made.

22 Therefore, your read-across approach under Annex XI, Section 1.5. is rejected. You remain responsible for complying with this decision by the set deadline.

Reasons related to the information under Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

23 An in vitro cytogenicity study in mammalian cells or an in vitro micro-nucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

1.1. Information provided

24 You have adapted this information requirement by using a Grouping of substances and read-across approach in order to meet the criteria of Column 2 of Annex VIII, Section 8.4.1. To support the adaptation, you have provided following information:

(i) a non guideline *in vivo* cytogenetic study over three generations in rats (1981) with the analogue substance 1,3-butanediol (EC 203-529-7)

(ii) a non-guideline Rodent dominant lethal test in rats (1981) with the analogue substance 1,3-butanediol (EC 203-529-7)

1.2. Assessment of the information provided

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

1.2.1. Read-across adaptation rejected

26 As explained in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

27 In the comments to the draft decision, you indicate your intention to improve the read-across approach using new source substances, but you have not provided any further information. Without this information, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

28 In addition, ECHA identified endpoint specific issue(s) addressed below.

1.2.2. Source study (i) not adequate for the information requirement

29 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 475. Therefore, the following specifications must be met:

a. The study must include a minimum of three doses/groups of treated animals, as well as a negative control group and a positive control group.
b. Each group must have a minimum of 5 analysable animals of one sex, or of each sex if both are used, per group (the test can be performed in either sex).
c. At least 200 metaphases per animal must be analysed for structural chromosomal aberrations including and excluding gaps.

30 The study (i) is described as an *in vivo* cytogenetic study over three generations. However, the following specifications are not according to the requirements of OECD TG 475:

a. No positive control group.
b. A minimum of 5 animals of one sex, or of each sex if both are used, per group since

only 2 males and 2 females were tested per group.

c. The analysis of the adequate number of cells since only 100 to 250 metaphase cells were examined *per group* instead of at least 200 metaphases *per animal*.

In the comments to the draft decision, you acknowledge the above deficiencies.

31 Based on the above, study (i) does not provide an adequate and reliable coverage of the key parameters addressed by the OECD TG 475 and this study is not an adequate basis for your read-across predictions.

1.2.3. Column 2 adaptation criteria not met by study (ii)

32 Under Section 8.4.2., column 2 of Annex VIII to REACH, the study usually does not need to be conducted "if adequate data from an in vivo cytogenicity test are available". The Guidance on IRs and CSA, Section R.7.7.6.3 and Table R.7.7–3 clarifies that the in vivo somatic cell cytogenicity test must be either a micronucleus test or a chromosomal aberration test, performed according to OECD TG 474 or 475, respectively.

33 You have provided a non-guideline Rodent dominant lethal test in rats (1981), study (ii).

34 The dominant lethal mutations detected by OECD TG 478 are generally the result of structural and/or numerical chromosomal aberrations. This study is an in vivo cytogenicity test, however it is performed on germ cells. Therefore, the results of such test cannot be used for the first level of classification as germ cell mutagen, i.e. category 2. Indeed in vivo data obtained on somatic cells is necessary for this purpose.

35 Moreover, for the data to be considered adequate, the in vivo cytogenicity test you submitted has to meet the requirements of OECD TG 478, and the specifications/conditions of this test guideline include:

a. A concurrent positive control group must be included in the study. The positive control substance must produce dominant lethal effects under the conditions used for the test.

36 The reported data for the in vivo study you submitted did not include:

a. Concurrent positive control animals.

37 In the comments to the draft decision, you acknowledge the above deficiency.

38 The information provided does not cover specifications/conditions required by OECD TG 478.

39 Based on the above, the column 2 criteria are not met.

1.3. Specification of the study design

40 To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

2. Screening for reproductive/developmental toxicity

41 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

2.1. Information provided

42 You have adapted this information requirement by using a Grouping of substances and read-across approach. To support the adaptation, you have provided following information:

(i) a non-guideline five-generation feeding study in rats (1981) with the analogue substance 1,3-butanediol (EC 203-529-7)

2.2. Assessment of the information provided

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

2.2.1. Read-across adaptation rejected

44 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

45 In the comments to the draft decision, you indicate your intention to improve the read-across approach using new source substances, but you have not provided any further information. Without this information, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

46 In addition, ECHA identified endpoint specific issue(s) addressed below.

2.2.2. Source study not adequate for the information requirement

47 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 421. Therefore, the following specifications must be met:

a. examination of parameters for sexual function and fertility such as those for mating and fertility, duration of gestation, parturition, lactation, and weight and histopathology of reproductive organs and tissues.
b. examination of offspring parameters such as number and sex of pups, stillbirths and live births, gross abnormalities, pup body weight, litter weight, anogenital distance, number of nipples/areolae in male pups.
c. terminal organ and body weights, gross pathology and full histopathology as specified in OECD TG 421.

48 The study (i) is described as a reproduction and teratology study. However, the following specifications are not according to the requirements of OECD TG 421:

a. Information on parameters for sexual function. In particular, you indicate in your dossier that examination of the parental generation is insufficient and the following investigations are missing: histopathological examination of sexual organs.
b. Information on offspring parameters. In particular, the following investigations are missing: anogenital distance in all pups, number of nipples/areolae in male pups. Furthermore, no terminal investigation or examination was performed in pups at postnatal days 4 and 13.
c. data on terminal organ weights and organ/body weight ratios, gross pathology findings and histopathology findings. In particular, the following investigations are missing: thyroid examination in pups and adult animals, necropsy of dams and pups on postnatal day 13.

49 In the comments to the draft decision, you acknowledge the above deficiencies.

50 Based on the above, study (i) does not provide an adequate and reliable coverage of the key parameters addressed by the OECD TG 421 and this study is not an adequate basis for your read-across predictions.

2.3. Specification of the study design

51 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

52 The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

53 Therefore, the study must be conducted in rats with oral administration of the Substance.

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 14 December 2020.

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

In your comments to the draft decision, you indicate your intention to update the registration tonnage band of your registration.

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 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]

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

(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 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.

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