~~Confidential~~

Helsinki, 6 May 2022

**Addressees**
Registrants of Diisopentyl ether as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**
29/10/2020

**Registered substance subject to this decision ("the Substance")**
Substance name: Diisopentyl ether
EC number: 208-857-4

**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 ***12 February 2024***.

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 vivo mammalian alkaline comet assay (Annex VIII, Section 8.4., column 2; test method: OECD TG 489) in rats, or if justified, in other rodent species, oral route, on the following tissues: liver, glandular stomach and duodenum;

   OR

   Transgenic rodent somatic and germ cell gene mutation assays (Annex VIII, Section 8.4., column 2; test method: OECD TG 488 from 2020) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach; duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.

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

**Reasons related to the information under Annex VIII of REACH**

## 1. In vivo mammalian alkaline comet assay or Transgenic rodent somatic and germ cell gene mutation assays

1 Under Annex VIII, Section 8.4, column 2 of REACH, the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

2 Your dossier contains positive results for the *in vitro* gene mutation study in bacteria (OECD TG 471, 2012) and *in vitro* cytogenicity test (OECD TG 487, 2012) which raise the concerns for gene mutation and chromosomal aberration.

3 In the comments to the draft decision, you indicate your intention to update the registration dossier with results from new *in vitro* gene mutation studies in bacteria with the Substance and negative data from the analogue substances dibutylether and diisopropylether.

4 However, the new study results on the Substance and a justification as to how and why the information on the analogue susbtances can be used to predict the mutagenicity potential of the Substance, or why this information would override the positive results mentioned above are currently not available in the registration dossier and cannot be assessed. Therefore, the concern for gene mutation raised by the positive *in vitro* gene mutation study in bacteria with the Substance remains.

5 Also, your dossier contains the following *in vivo* study:

(i) *In vivo* micronucleus test (OECD TG 474, 2012) with the Substance

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

7 In order to be appropriate, according to ECHA Guidance R.7a, the *in vivo* somatic cell genotoxicity study must address the specific concerns raised by the *in vitro* positive result.

8 However, the *in vivo* study provided investigates chromosomal aberration only and is not addressing the gene mutation concern raised by the *in vitro* data. Therefore, the provided *in vivo* test is not appropriate for this endpoint.

9 ECHA considers that an appropriate *in vivo* follow up mutagenicity study is necessary to address the gene mutation concern identified *in vitro*.

10 In the comments to the draft decision, you propose to adapt this information requirement, arguing that the Substance is used in industrial settings only, unreactive, and approved for use as a food additive under the Japanese jurisdiction and animal testing should be avoided.

11 You have not provided any legal basis for your adaptation. For example, approval of the Substance for use as a food additive under the Japanese jurisdiction does not mean that the supporting data are compliant with REACH since it applies different rules and follows different objectives. Also, you have not explained why this information would be relevant under REACH and you acknowledge the fact that the specific supporting data are not available.

12 Therefore, your adaptations are rejected and you remain responsible for complying with this decision by the set deadline.

### *1.1. Test selection*

13 According to the ECHA Guidance Chapter R.7a, Section R.7.7.6.3, either the transgenic rodent somatic and germ cell gene mutation assay ("TGR assay", OECD TG 488) or the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a positive *in vitro* result on gene mutation.

*1.2. Test design*

14 In case you decide to perform the comet assay according to the test method OECD TG 489, rats are the preferred species. Other rodent species can be used if scientifically justified (OECD TG 489, para. 23).

15 Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate.

16 In line with the test method OECD TG 489, the test must be performed by analysing tissues from the liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

17 In case you decide to perform the TGR assay according to the test method OECD TG 488, the test must be performed in transgenic mice or rats and the test substance is usually administered orally.

18 Based on the recent update of OECD TG 488 (2020), you are requested to follow the new 28+28d regimen, as it permits the testing of mutations in somatic tissues and as well as in tubule germ cells from the same animals.

19 According to the test method OECD TG 488, the test must be performed by analysing tissues from the liver as slowly proliferating tissue and primary site of xenobiotic metabolism, glandular stomach and duodenum as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 ºC) until the analysis of liver and glandular stomach is completed; the duodenum must then be analysed only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

*1.2.1. Germ cells*

20 In case you decide to perform the comet assay, you may consider to collect the male gonadal cells collected from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, you should consider analysing the slides prepared with gonadal cells.

21 In case you decide to perform the TGR, you may consider to collect the male germ cells (from the seminiferous tubules) at the same time as the other tissues, in order to limit additional animal testing. According to the OECD 488, the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 ºC). This duration is sufficient to allow you or ECHA, to decide on the need for assessment of mutation frequency in the collected germ cells.

22 This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

## 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 09 July 2021.

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

In your comments to the draft decision, you raised the issue of updating the registration tonnage band of your registration.

ECHA took into account your comments and did not amend the request(s) and the deadline.

> You requested 5 months to update your dossier. Since the deadline set is 18 months from the date of the decision, no additional time is deemed necessary.
>
> ECHA has not modified the deadline.

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

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

**Appendix 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 Annexes VII and VIII to REACH, for registration at 10-100 tpa.

| Registrant Name | Registration number | Highest REACH Annex applicable to you |
|---|---|---|
| [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

(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