ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 21 December 2018

Addressee: [redacted]

Decision number: CCH-D-2114453661-50-01/F
Substance name: Oligomerisation products of beta-pinene
EC number: 701-246-8
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 03/05/2018
Registered tonnage band: [redacted]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14./OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance provided that the study requested under 1 has a negative result;**

3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**

4. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

5. **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 registered substance;**

6. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance;**

You have to submit the requested information in an updated registration dossier by **28 June 2021**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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] by **Claudio Carlon**, Head of Unit, Evaluation **E2**

[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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1, 2, 3, 5).

0. Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- *in vitro* gene mutation study in bacteria (Annne VII, Section 8.4.1)
- *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3)
- sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance Oligomerisation products of beta-pinene (EC No: 701-246-8) using data of structurally similar substances:

- 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5); and
- 7-Methyl-3-methylene-1,6-octadiene (β-myrcene) (EC No 204-622-5)
- 2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (alpha-pinene) (EC No 201-291-9)(hereafter the 'source substances').

You refer to the source substances as "close analogues" of the registered substance or "phytoterpene analogues". Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical and toxicological properties between the source and registered substances is a sufficient basis for predicting the properties of the registered substance for other endpoints. You argue that the registered substance is a cyclic phytoterpene, the monomer units of which are directly comparable to 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5) and 2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (alpha-pinene) (EC No 201-291-9) and that the phytoterpene 7-Methyl-3-methylene-1,6-octadiene (β-myrcene) (EC No 204-622-5) is a close analogue sharing the coupled isoprene units that make up terpenes, although it is non-cyclic. ECHA rejects this aspect of your read-across justification. The proposed source substances differ considerably in chemical structure from the constituents of the UVCB target substance, as the latter is an oligomerisation product. In addition you failed to provide explanation on the potential impact of the difference in structure of the source substances to the beta-pinene monomer that is polymerised to form the registered oligomer substance. You further argue that the target and source substances share generally comparable physico-chemical properties and are of low acute toxicity, although the water solubility and logKow differ due to the higher molecular size of the target substance. Additionally, ECHA notes that similarity in chemical structure and similarity of some of the physico-chemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints.

In your comments on the draft decision you restate that in your view read-across from

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

monomers to an oligomeric target substance is valid and you remark that you consider that ECHA's RAAF is not wholly appropriate to UVCB substances. However, you do not address the shortcomings in the read-across justification identified by ECHA: (a) the proposed source substances differ considerably in chemical structure from the constituents of the UVCB target substance, as the latter is an oligomerisation product, (b) there is no discusson on the impact of the difference in structure of the source substances to the beta-pinene monomer that is polymerised to form the registered oligomer substance and (c) the target and source substances differ in water solubility and log Kow.

Therefore, taking into account the above arguments and your comments, your justification based on structural similarity, similar physico-chemical, ecotoxicological and toxicological properties has not established why the prediction is reliable for the human health end-points for which the read across is claimed.

Therefore, your dossier is lacking a basis for predicting relevant human health properties of the registered substance from data for the source substances.

Hence, you have not established that relevant properties of the registered substance can be predicted from data on the analogue substances. Since your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., it is rejected and it is necessary to perform testing on the registered substance.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. 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 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1994 according to OECD TG 471 and GLP with an assigned reliability score of 1. The test used five different strains of S. typhimurium TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

Additionally, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an *in vitro* gene mutation in bacteria (OECD TG 471), using strains TA 98, TA 100 E Coli pKM 101, with the analogue substance 2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (alpha-pinene) (EC No 201-291-9). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

In your comments on the draft decision you indicated that there is already a study on the missing strain with the analogue substance, nevertheless you agreed to conduct the Ames study on the fifth strain of bacteria with the registered substance.
As explained above, the read-across cannot be accepted. Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.
ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14./OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an *in vitro* gene mutation in mammalian cells (OECD TG 476) from 1990 using mouse lymphoma cells, reliability 2, with the analogue substance d-4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5).

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

In your comments on the draft decision you indicated that the read-across approach to limonene should be considered acceptable. Moreover, you refer to a negative *in vivo* micronucleus assay and a rat liver UDS with the analogue substance. Nevertheless, as a final comment you agreed to conduct the *in vitro* mammalian mutagenicity assay.

ECHA notes that none of these *in vivo* studies are relevant for the assessment of this standard information requirement as per Annex VIII Section 8.4.3. studies because of the following:

(i.) As explained in Appendix 1, under the *Grouping of substances and read-across approach* section of this decision, the information requirement according to Annex XI, Section 1.5. of the REACH Regulation is currently not met; and

(ii.) The *in vivo* micronucleus study referred to in your comments does not address gene mutation (but chromosome aberration) while the liver unscheduled DNA synthesis (UDS) assay provides only an indication of induced DNA damage followed by DNA repair (but not direct evidence of mutation). Moreover, according to the ECHA's Guidance[4], a negative result in a UDS assay alone is not a proof that a substance does not induce gene mutation, and so this *in vivo* study does not provide an adaptation for the lack of an *in vitro* gene mutation study.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the Hprt and xprt genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information

[4] ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance, Section R.7.7.6.3, Version 6.0

requirement of Annex VIII, Section 8.4.3.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under 1. has negative results.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following information:

1. a study record for an oral sub-chronic toxicity study (90-day) (OECD TG 408) in rat, with the analogue substance 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5). The test was conducted in 1990 and was assigned a reliability score of 2.
2. a study record for an oral sub-chronic toxicity study (90-day) (OECD TG 408) in mouse, with the analogue substance 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5). The test was conducted in 1990 and was assigned a reliability score of 2.
3. a supporting study record for an oral short-term toxicity study (30-day) in rat (no guideline followed), with the analogue substance 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5). The test was conducted in 1977 and was assigned a reliability score of 4.

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Moreover, ECHA notes that study 3 above is not performed according to GLP and does not follow any test guideline. Annex XI, section 1.1.2. provides that test data from experiments not carried out according to GLP shall be considered equivalent to data generated in accordance with the relevant test methods referred to in Article 13(3) REACH if the conditions set out in Annex XI , section 1.1.2. are met. This study fails to meet the second and third conditions set out in Annex XI, Section 1.1.2. since it does not provide adequate and reliable coverage of key parameters foreseen to be investigated in the corresponding OECD test guideline 408. More specifically, study 3 does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, the sensitivity of a short-term study is much lower than that of a 90-day study.

In your comments on the draft decision you indicated that the read-across approach to limonene should be considered acceptable. Nevertheless, you agreed to perform the sub-chronic (90-day) study. In particular you agreed that the oral route is the appropriate route of exposure.
As explained above, the read-across cannot be accepted. Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of low vapour pressure. Uses with professional and consumers spray application are reported in the chemical safety report. However, appropriate risk management measure are in place (including the use of gloves, impermeable protective suit, head covering, eye/face and respiratory protection) to prevent professional workers' exposure during spraying applications. Additionally, in the case of consumer spraying use, the reported concentrations are low (<1%). Hence, the test shall be performed by the oral route using the test method OECD TG 408.

According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex VIII, Section 8.7.1. or with the general rules of Annex XI for this standard information requirement.

In your comments on the draft decision, you refer to the one-generation reproductive toxicity study (OECD TG 415) on the proposed source substance β-myrcene. ECHA notes that this study cannot be used to fulfil this particular endpoint because the read-across from the source substance is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid with a low vapour pressure, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:
- Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

ECHA notes that in your comments you also indicated that you will update the dossier with a waiver justification for this endpoint when a pre-natal developmental toxicity study is available (requested in Section 5 of the present decision). As indicated in the "*Notes for your consideration*" (hereunder) if a valid pre-natal developmental toxicity study is available, you can waive the Screening for reproductive/developmental toxicity study according to Annex VIII Section 8.7.1.

Notes for your consideration

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017."

5. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following information:

1. a study record for a pre-natal developmental toxicity study (OECD TG 414) in rat, with the analogue substance 7-Methyl-3-methylene-1,6-octadiene (β-myrcene) (EC No 204-622-5). The test was conducted in 1993 and was assigned a reliability score of 2.
2. a study record for "peri- and postnatal developmental toxicity of beta-myrcene in the rat" (no guideline followed), with the analogue substance 7-Methyl-3-methylene-1,6-octadiene (β-myrcene) (EC No 204-622-5). The test was conducted in 1993 and was assigned a reliability score of 2.
3. a study record for a chronic toxicity study in rats (no guideline followed), with the analogue substance 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5) in rat. The test was conducted in 1975 and was assigned a reliability score of 4.
4. a study record for a study on the effect on development of rabbit foetuses and offsprings (no guideline followed), with the analogue substance 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5) in rabbit. The test was conducted in 1977 and was assigned a reliability score of 4.
5. a study record for a study on the effect on development of mouse foetuses and offsprings (no guideline followed), with the analogue substance 4-isopropenyl-1-methylcyclohexene (d-limonene) (EC No 227-813-5) in mouse. The test was conducted in 1977 and was assigned a reliability score of 4.

However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Moreover, ECHA notes that studies 2 to 5 above are not performed according to GLP and do not follow any test guidelines. Annex XI, section 1.1.2. provides that test data from experiments not carried out according to GLP shall be considered equivalent to data generated in accordance with the relevant test methods referred to in Article 13(3) REACH if the conditions set out in Annex XI , section 1.1.2. are met. These studies fail to meet the second, third and fourth conditions set out in Annex XI, Section 1.1.2. since they do not provide adequate and reliable coverage of key parameters foreseen to be investigated in the corresponding OECD test guideline 414. The exposure duration is shorter than in the corresponding test method referred to in Article 13(3), and they do not provide adequate and reliable documentation. More specifically, the "peri- and postnatal developmental

toxicity of beta-myrcene in the rat" (study 2) does not provide the information required by Annex IX, Section 8.6.2., because the dams were not administered from implantation (e.g. day 5 post mating), the exposure duration period of dams is less than in a pre-natal developmental toxicity study and the number of animals per dose group is lower than in a pre-natal developmental toxicity study (OECD TG 414). Therefore, the sensitivity of the "peri- and postnatal developmental toxicity of beta-myrcene in the rat" is much lower than that of a pre-natal developmental toxicity study. Moreover, various shortcomings were noted for studies 3 to 5 above, namely: no information was provided on the dose levels and on the size of the dose groups; the dams were not administered from implantation (e.g. day 5 post mating); and the exposure duration period of dams is less than in a pre-natal developmental toxicity study. Therefore, the sensitivity of studies 3 to 5 is much lower than that of a pre-natal developmental toxicity study (OECD 414).

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid with a low vapour pressure, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision you indicated your disagreement to ECHA's read-across assessment, however you also stated that the read-across for this endpoint is not that strong and you agreed to perform the study with the registered substance via the oral route. As explained above, ECHA notes that the current read-across cannot be accepted. Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

6. Identification of degradation products (Annex IX, 9.2.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The biodegradation section in the technical dossier does not contain any information in relation to the identification of degradation products, nor an adaptation in accordance with column 2 of Annex IX, Sections 9.2 or 9.2.3. or with the general rules of Annex XI for this standard information requirement.

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable.

Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding appropriate and suitable test method, the methods will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You may obtain this information from the a simulation study or by some other measure. You will need to provide a scientifically valid justification for the chosen method. If you choose to undertake a simulation study for the purpose of identification of degradants, ECHA notes that the aerobic and anaerobic transformation in soil (test method EU C.23. / OECD TG 307) is the preferred test, because the substance has a high potential for adsorption to soil (i.e. logKoc >4) and there is direct exposure of the substance to soil. Simulation tests performed in sediment or in soil possibly imply the formation of non-extractable residues (NER). These residues (of the parent substance and/or transformation products) are bound to the soil or to the sediment particles. NERs may potentially be re-mobilised as parent substance or transformation product unless they are irreversibly bound or incorporated into the biomass. When reporting the non-extractable residues (NER) in your test results you are requested to explain and scientifically justify the extraction procedure and solvent used obtaining a quantitative measure of NER.

In your comments on the draft decision, you explain that it will be difficult to fulfil this information requirement for this UVCB substance that is of natural origin because (a) identification of oligomers and isomers in the substance and degradation products is analytically challenging, (b) based on previous experience, it will be difficult to distinquish these from naturally occurring terpenes and (c) radio-labelled test material cannot be prepared because the registered substance is derived from a starting material of natural origin.

ECHA re-iterates the principles for providing information on identification of degradation products. You can choose to undertake a simulation test as a means of providing information on degradation products. If you do this, the aerobic and anaerobic transformation in soil test (OECD 307) is the most appropriate simulation test, i.e. it is less appropriate to use the aerobic mineralisation in surface water – simulation biodegradation test (OECD 309) or the aerobic and anaerobic transformation in aquatic sediment systems test (OECD 308). Alternatively you can provide information on identification of environmental degradation products by other means, for example perhaps as a weight of evidence using experimental results and arguments based on the chemical and physical properties of the constituents of the registered substance. Nevertheless, in spite of the

analytical challenges to extract from environmental matrices and to identify and to quantify the constituents of the UVCB registered substance and environmental transformation products, it is your responsibility to provide adequate information on what happens to the substance in the environment.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

Notes for your consideration

Before providing the above information you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R.7b., Sections R.7.9.2.3 and R.7.9.4. These guidance documents explain that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section R.7.9.4. further states that when substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 19 June 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

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 took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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 your Member State.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.