EUROPEAN CHEMICALS AGENCY

Helsinki, 26 May 2020

Addressees
Registrants of Dicyclopentadiene (LOA) listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
14/05/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 3a,4,7,7a-tetrahydro-4,7-methanoindene
EC number: 201-052-9
CAS number: 77-73-6

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 the deadlines provided.

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

1. Sub-chronic toxicity study (90-day), oral route by gavage (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats with the Substance modified to include urinalysis and immune-histochemical investigation of renal pathology;

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 by gavage 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 Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

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

The Appendices state 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 point A.1 above in an updated registration dossier by **31 August 2021**, and the information requested in point A.2 above by **31 August 2022**.

You must 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 A: Reasons for the requests to comply with 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 under Annex IX to REACH.

You have provided the following studies for this endpoint in your dossier:

Key studies

i. Combined repeated dose and reproductive/developmental toxicity screening test in rats via oral route (equivalent or similar to OECD 422, GLP, 1993)
ii. 90-day study in rats via inhalation route (equivalent or similar to OECD 413, no GLP, 1982)
iii. 90-day study in mice via inhalation route (equivalent or similar to OECD 413, no GLP, 1982)

Supporting studies

iv. 90-day study in dogs via oral route (equivalent or similar to OECD 409, no GLP, 1980)
v. 90-day study in rats via inhalation route (equivalent or similar to EPA OTS 798.2450, no GLP, 1971)

In the draft decision notified to you, we had assessed this information and identified the following issue:

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408 or 413. The following key parameter(s) of these test guidelines include, among others

- testing in rodents
- highest dose level should aim to induce some systemic toxicity, but not death or severe suffering
- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study
- ophthalmological examination, haematology and clinical biochemistry
- pathology of sexual (male and female) organs and full detailed gross necropsy and subsequent histopathology of both types tissues.

The studies you have provided were not performed according to the criteria of the OECD TG 408 or 413, since the following key parameters are missing:

- Study i. does not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 44 days for males and for females from 14 days before mating through gestation and parturition until day 3 of lactation.
- In studies ii. and iii., histopathological examination was not adequate as it excluded e.g. histopathology of ovaries, uterus and mammary gland. In addition, gross necropsy was insufficient as only organ weights of kidneys, lung, liver and testes were recorded and other organs excluded from weight measurement.

- Study iv. is not conducted in rodents as required in OECD TG 408 and 413 and by Section 8.6.2. of Annex IX of REACh. In addition, no toxicity was observed.
- In study v. Gross necropsy was not adequate as organ weights were not adequately studied, only weights of kidneys and liver were recorded. In addition, ophthalmological examination, haematology and clinical biochemistry were not performed.

In your comments to the draft decision, you considered that since four 90-day studies with the Substance in three different species are already submitted, application of a Weight of Evidence approach should be sufficient to satisfy REACH information requirement for sub-chronic toxicity study (Annex IX, Section 8.6.2.).

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

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

However, for each relevant information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation and identified the following issues.

To fulfil the information requirement, normally a study according to OECD TG 408 or 413 must be provided. The key parameters investigated by these tests include a full, detailed gross necropsy including mandatory weighing of 13 organs, histopathology of all gross lesions and of about 40 organs and tissues, haematology and clinical biochemistry examinations. REACH (Annex IX, Section 8.6.2.) also provides that the testing should be done in rodents.

In your weight of evidence approach, you refer to four 90-day studies ((ii) – (vi) in the draft decision). However, the reliability of the pieces of information (i)-(vi) is affected bydeficiencies specified in the draft decision and still not addressed in your comments. Briefly, none of the 90-day studies in rodents had the organs weights measured for other organs than kidneys, liver, lung and testes (versus 13 organs specified in the OECD TG 408 or 413), in the key studies in rats (ii) and mice (iii) the histopathology of ovaries, uterus and mammary gland was not performed (essential organs to derive information on potential reproductive toxicity in females), one supporting study (iv) was performed in dogs (not the species requested by REACH) and using too low doses, and the other supporting study in rats (v) had no investigation on haematology, clinical biochemistry and ophthalmological examinations (mandatory key parameters of a 90-day study). Thus, ECHA notes that even if the studies (ii) - (vi) are considered together they do not cover all the required key parameters as the full,

detailed gross necropsy is lacking and the weights of only very few organs were recorded in (ii), (iii) and (v) as explained above. Although more extensive gross necropsy was performed in study (iv), it was conducted according to OECD TG 409 in dogs and with too low doses with no systemic toxicity observed with the highest dose. In addition, there is no 90-day rodent study via the oral route. However, an available Combined repeated dose and reproductive/developmental toxicity screening test via oral route in rats (i) shows an additional concern for systemic toxicity, i.e. histopathological findings in adrenals.

Based on the assessment above, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in OECD TG 408 or 413 studies. Your adaptation is rejected.

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

Furthermore, you considered that conducting a fifth 90-day study is not ethical for animal welfare reasons, nor is it aligned with the REACH principle of vertebrate animal testing as a last resort. ECHA notes that due to the deficiencies highlighted above there is data gap in the standard information requirement for sub-chronic 90-day toxicity study (Annex IX, Section 8.6.2.) that must be filled.

Information on the design of the study to be performed

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity and the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration for the following reasons. The substance is a liquid and although the available information indicates that exposure of humans 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. In addition, the available Combined repeated dose and reproductive/developmental toxicity screening test via oral route in rats (1993) shows an additional concern for systemic toxicity, i.e. histopathological findings in adrenals. Increases in fatty droplets in the fascicular zone of adrenals were observed dose-dependently in male rats at the two highest dose levels of 20 (in 3 of 10 animals) and 100 mg/kg bw/day (in 8 of 10 animals). A similar adrenal effect was observed in female rats at the highest dose level. No adrenal effects were reported in any of the provided repeated dose toxicity studies via the inhalation route. This suggests an oral route-specific toxic effect on adrenals that requires further information on subchronic repeated dose toxicity by the oral route. The study should be performed by oral gavage, as this was the method of oral dosing in the Combined repeated dose and reproductive/developmental toxicity screening test in rats (1993) which showed adrenal effects, and it is necessary to use the same dosing method (i.e. oral gavage) in order to investigate any effect on adrenals. An additional reason for the use of oral gavage is the potential for volatilisation either of the principal constituent, dicyclopentadiene, or of any impurities that may be toxicologically important. For these reasons, the homogeneity and stability of the test chemical under the conditions of administration (paragraph 14 of OECD TG 408) must be reported in the respective endpoint study record, under the Test material section.

In your comments on the draft decision you indicated that it is unclear why another 90-day study in rat is requested while the mouse appears to be the most sensitive (rodent) species and is driving the long-term inhalation DNEL for both local and systemic effects. The request for a new 90-day study in rats is based on the effects observed in adrenals in rats via oral route in the provided screening study as explained above. Toxicokinetic data in the dossier

indicates that the Substance is rapidly absorbed via oral route in rats. In addition, adrenals were one of the organs in which the highest concentrations of the Substance were found after a single oral dose.

In the 90-day inhalation study in rats (1982) you indicate that the Substance "*produced kidney damage in male rats at all dose levels. There were epithelial cells excreted in the urine and alterations in kidney structure in the proximal tubule, such as an increase in the incidence of hyaline droplets, regenerative epithelium, and an accumulation of tubular proteinaceous material. From electron micrographs, many of the hyaline droplets in the exposed male rats appeared electron-dense and angular or crystalline-shaped. These kidney effects were not observed in any of the female rats and were not observed post-exposure or at the end of the recovery period.*" Thus, adverse effects were observed in the kidneys of male rats but not in male control rats or in any exposed/control female rats.

This indicates that the kidney is a target organ of the Substance which may induce alpha-2u-globulin-mediated nephropathy. Since this mode of action is considered not relevant to humans, the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment.

In your comments on the draft decision, you found it astonishing that the requested sub-chronic (90-day) oral toxicity study in rats should include urinalysis and immune-histochemical investigation of renal pathology to determine if the renal pathology seen in the available rat studies is mediated by alpha-2u globulin. You stated that the evidence seen in the studies is very strong and this mode of action is considered not to be relevant for humans. You referred to the publication by [redacted] (1992) in which these findings are discussed in detail. You stated also that these findings are discussed in the registration dossier. ECHA notes that the fact that the kidney effects were only observed in male rats indicates that the Substance may, indeed, induce alpha-2u globulin-mediated nephropathy and that this mode of action is not relevant for humans as explained above. However, the information provided in the dossier does not have any direct evidence to show that the observed renal pathology in male rat is mediated by alpha-2u globulin.

Therefore, although optional (as per paragraph 37 of OECD TG 408), a urinalysis is required to investigate further the kidney function after administration of the Substance. Additionally, a full histopathological examination (paragraphs 3, 45 and 47 of OECD TG 408), including immune-histochemical investigation of renal pathology is required to determine if the pathology is mediated by alpha-2u globulin.

You provided comments on the Proposal for Amendment (PfA) submitted by one of the Member States Competent Authorities (MSCAs), regarding Appendix C.5, referring to characterisation of the Test Material. Firstly, you propose that the substances mentioned in the PfA are not present in the Substance and you are unaware of any registration "*with these substances in any significant portion*". Secondly, you indicate a wish to test a purified substance with high purity DCPD, and that this would be the most representative test material.

In respect of the first issue, we note that there is no need to test where you have a robust basis to exclude the presence of a constituent/impurity. ECHA notes that impurities, such as 2-methylbut-2-ene (EC no. 208-156-3), 4-vinylcyclohexene (EC no. 202-848-9), toluene (EC no. 203-625-9) and benzene (EC no. 200-753-7; CAS no. 9072-35-9), are listed in individual dossiers. Thus, when selecting the test material you will need to take into account this fact. In respect of the second issue, we agree that it may be a viable strategy to test the more highly purified DCPD. However, ECHA notes that the registration allows for non-DCPD

constituents/impurities up to 20%, and it would be incumbent on you to identify what these non-DCPD constituents/impurities are, and to justify how these non-DCPD constituents/ impurities affect the properties of the Substance.

ECHA has therefore, amended point 7 of the Appendix C to reflect that the PfA concerns the technical reporting of the test material.

Deadline to submit the requested information under point A.1 of the decision

The deadline indicated in the draft decision to provide the information requested under point A.1 (Sub-chronic toxicity study (90-day)) was 12 months from the date of adoption of the decision. In your comments on the draft decision, you considered that it is not possible to update the dossier within 12 months with data from the requested 90-day study due to inclusion of urinalysis and immune-histochemical investigation of renal pathology. You indicated that an additional 6-12 months will be required to complete the study, i.e. the deadline for 90-day study should be 18-24 months. ECHA notes that the documentation submitted by you contained insufficient evidence as to why the deadline would need to be extended. Following your comments, ECHA requested you on 3 September 2019 to submit documentary evidence from the selected test laboratory in order to justify why an extension to the stated deadline of 12 months would be necessary. You did not, however, provide any further information to support the extension of the given deadline. Therefore, ECHA has not modified the deadline.

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

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

You have provided the following studies for this endpoint in your dossier:

Key study

i. A dietary prenatal developmental toxicity study in rats (equivalent or similar to EPA OPP 83-3 prenatal developmental toxicity study, no GLP, 1978)

Supporting studies

ii. Dose range finding study for developmental toxicity in rats (no guideline followed, GLP compliant, 1993)
iii. Dose range finding study for developmental toxicity in rabbits (no guideline followed, GLP compliant, 1993)

We have assessed this information and identified the following issues:

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the study has to meet the requirements of OECD TG 414. The key parameter(s) of this test guideline include:

- the highest dose level should aim to induce some developmental and/or maternal toxicity.
- examination of the foetuses for external, skeletal and soft tissue alterations (variations and malformations).

In ECHA's decision CCH-D-2114313205-65-01/F (11 December 2015), further information in the form of a robust study summary on the dietary prenatal developmental toxicity study (i) in rats (1978) was requested. You provided an improved robust study summary and also included a study report in an updated dossier (submission number [redacted]) on 14 May 2018. However, you have not reported all the required data as listed in the section III "Statement of reasons" of the original decision, and in particular have not reported the dose selection rationale. You have reported that the highest test substance concentration measured in the diet (750 ppm) corresponds to a dose of 60 mg/kg bw/day. The highest dose level in the study (i) did not induce any developmental and/or maternal toxicity and you have not shown that the aim was to induce toxicity. Therefore, the dose level selection was too low, and the study does not fulfil the criterion set in OECD TG 414.

In addition, foetuses were not examined for external, skeletal and soft tissue alterations (variations and malformations) in the provided supporting studies (ii and iii) as required in OECD TG 414. Furthermore, in the provided combined repeated dose and reproductive/developmental toxicity screening test in rats via oral route (1993), you reported lower viability index and birth weight in the offsprings at 100 mg/kg bw/day. These effects are of concern and need to be followed up in a definitive pre-natal developmental toxicity study.

Therefore, the provided studies do not fulfil the information requirement.

Information on study design

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[2] administration of the Substance. The study should be performed by oral gavage, as this was the method of oral dosing in the Combined repeated dose and reproductive/developmental toxicity screening test in rats (1993) which showed developmental effects, and it is necessary to use the same dosing method (i.e. oral gavage) in order to investigate any developmental effects. An additional reason for the use of oral gavage is the potential for volatilisation either of the principal constituent, dicyclopentadiene, or of any impurities that may be toxicologically important. For these reasons, the homogeneity and stability of the test chemical under the conditions of administration (paragraph 39 of OECD TG 414) must be reported in the respective endpoint study record, under the Test material section.

In your comments to the draft decision, you indicated your agreement to conduct the requested study and considered to perform the first species PNDT study (OECD 414) in rabbits. ECHA notes that the first species PNDT study is requested in this present decision and the request for the second species PNDT study is notified to you in a separate decision on a testing proposal. It is at your discretion to decide which species you want to test first.

You provided comments on the PfA, regarding Appendix C.7, referring to characterisation of the Test Material. Your comments have been addressed under Appendix A.1.

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

Appendix B: 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 08 November 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 within 30 days of the notification.

ECHA took into account your comments and did not amend the requests and the deadline.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-69 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix C: Observations and technical guidance

1. The Substance subject to the present decision is listed in the Community rolling action plan (CoRAP).

2. The information requirement under Section 8.7.3. of Annex IX/X to REACH (Extended one-generation reproductive toxicity study, EOGRTS) is not addressed in this decision, because the information from the Sub-chronic toxicity study (90-day), requested in the present this decision, is relevant for the design of the EOGRTS.

3. A testing proposal on the 2nd species PNDT was submitted on 5 May 2018 and is addressed under the TPE decision.

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

5. 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.

6. 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[3]'.

7. 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, 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.

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

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.

There is the potential for the test material to include impurities which have carcinogenic, mutagenic or reprotoxic properties, such as (but not limited to) 2-methylbut-2-ene (EC: 208-156-3), toluene (EC: 203-625-9), mixed xylenes (EC: 292-694-9 and EC: 215-535-7), 4-vinylcyclohexene (EC: 202-848-9) and n-hexane (EC: 203-777-6). To the extent technically feasible, the presence and concentration values of such CMR constituents must be determined empirically in the test material, reported, and the relevance for the Substance, as a whole, justified.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[3].

8. List of references of the ECHA Guidance documents[4]

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)5

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.

[4] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] 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.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment

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 D: 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]