~~Confidential~~

Helsinki, 09 September 2021

**Addressees**
Registrant(s) of JS_IFF_OTNE as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**
18 November 2020

**Registered substance subject to this decision ("the Substance")**
Substance name: reaction mass of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one and 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one and 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one
EC number: 915-730-3
CAS number: NS

**Decision number:** Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

## DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-2114341495-48-01/F of 10 October 2016 ("the original decision") ECHA requested you to submit information by 17 April 2020 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

**Your registration still does not comply with the following information requirement(s):**

> **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit), oral route, with the registered substance**

You are therefore still required to provide this information requested in the original decision.

Reasons for the request are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annex X of REACH".

**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**

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision. They have the duty under Articles 125 and 126 of Regulation No 1907/2006 to ensure that the requests in the original decision are enforced and complied with and, to that end, inter alia, to carry out checks and impose effective, proportionate and dissuasive penalties[1].

Authorised[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] See paragraph 143 of the judgment of the European Court of Justice of 21 January 2021 in Case C-471/18 P Germany v Esso Raffinage

[2] 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 to request information required under Annex X of REACH

### 1. Pre-natal developmental toxicity study in a second species

You were requested to submit information derived with the registered substance ('the Substance') for Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in a second species (rabbit), oral route.

In the updated registration subject to follow-up evaluation, you have provided an oral PNDT study ([redacted], 2019) in rabbits, according to OECD TG 414, performed with the Substance. The doses used in the study were 0, 75, 200 and 500 mg/kg body weight/day, and the animals were exposed during gestation days (GD) 6-28. The mean body weight of the maternal animals at the highest dose (500 mg/kg bw/day) were slightly lower than controls (not statistically significant). At this dose level, the liver weights were increased, which according to you 'may be adaptive (increase due to metabolising the substance)'. For conservative reasons, you considered these effects to be adverse, and set the NOAEL at the mid dose tested (200 mg/kg bw/day).

*Dose level selection*

In order to be compliant, the information provided has to meet the requirements of OECD TG 414.

With regard to dose selection, OECD TG 414 states that "*the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering*".

You explain that the dose selection for the main OECD TG 414 study was based on an oral dose range finding (DRF) study on mated rabbits exposed to the Substance during GD 6-28, using doses of 0, 30, 120 and 500 mg/kg bw/day with 4 animals per dose group, and repeated dose toxicity studies with rats, with a reference to 'oral gavage 90-day study'. Your dossier contains an OECD TG 408 study (duration 90 days) in rats. Furthermore, you explain that the studies in rats were taken into consideration "not to overload the metabolic capacity too much for rabbits", and that "The dose levels are set on a tolerable liver weight increase of ca 25%."

In your comments, you refer to OECD TG 414, paragraphs 14 and 15, stating that for dose level setting, all available information should be considered. You explain that the available studies in rats (i.e. OECD TG 421 study with 54-day exposure as well as OECD TG 408 and NTP studies with 90 days exposure) showed relative liver weight increases up to 50%, which was considered to be adverse, and to be an interspecies phenomenon due to common metabolic pathways in mammals.

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

The duration, dose levels and test species in your DRF were comparable to the main OECD TG 414 study. There were no findings in the DRF, and the study report concluded that "*Based on the absence of any effects indicative for maternal toxicity (body weight, food consumption, clinical observations) an increase of the dose level should be considered for the subsequent main prenatal development study in rabbits.*" Based on these results and conclusions, ECHA considers that there is no reliable basis to assume that in the main OECD 414 study, maternal toxicity (clinical signs or a decrease in body weight) would be seen at 500 mg/kg bw/day.

In the OECD TG 408 study in rats, exposure to 500 mg/kg bw/day for 90 days resulted in an increase in relative liver weight of up to 50%. ECHA notes that you have not provided any

explanation why a 50% increase in liver weight in non-pregnant rats during 90-day exposure is estimated to result in 25% increase in liver weights in pregnant rabbits during 23 days of exposure.

In your comments, you explain that the metabolic pathways for bicyclic ketones are ubiquitous present in mammals. The similar metabolism is supported by the observed liver weight increase in rats and rabbits. Therefore, you consider the interspecies extrapolation from rat to rabbit to be justified, and that the OECD TG 414 study in rabbits is carried out with sufficient high doses.

ECHA notes that even though the metabolic *reactions* may be similar across mammalian species, the metabolic *rate* varies between species. In addition, the rat study durations are different from the PNDT study in rabbits. Therefore, the rat data does not directly inform on effects in rabbits. You haven't explained the basis of your predicted calculations extrapolated from (non-pregnant) rat to (pregnant) rabbit. Furthermore, ECHA notes that whilst all available information should be taken into account for the dose level setting, the DRF study in pregnant rabbits provides the most relevant information for an OECD TG 414 study in rabbits. As explained above, there were no findings in the DRF study in rabbits, up to 500 mg/kg bw/day.

With regards to metabolic capacity, ECHA notes that exceeding metabolic capacity is an intrinsic property of the substance and its consequences on development need to be investigated.

For the main OECD TG 414 study you reported that the mean body weight of the maternal animals at the highest dose (500 mg/kg bw/day) were ~5% lower than controls (not statistically significant). At this dose level, the liver weights were increased (absolute +9.8%, relative +16%**), which according to you 'may be adaptive (increase due to metabolising the substance)'. You reported that no test item-related clinical signs of toxicity were observed during the experimental period in any dose group, and that there was no test item-related mortality. You reported no developmental toxicity during the study.

In your comments, you emphasise the 'clear maternal effects (food consumption decrease, liver weight increase of 16%)' seen in the OECD TG 414 study. You consider that re-doing a (dose-range finding) developmental test would result in more (severe) suffering which should be avoided.

ECHA notes that in the OECD TG 414 study, the overall food consumption was slightly reduced at the high dose (500 mg/kg bw/day): -17% compared to controls. However, the food consumption at this dose level varied within time points, from -32% on GD 6-9 to +30% on GD 24-29 (compared to controls). The slight overall reduction in food consumption resulted in slightly lower body weights (~5%).

At 500 mg/kg bw/day, the absolute liver weight was increased by 9.8%. You consider this to be adaptive, not adverse. ECHA agrees.

ECHA concludes that the top dose in the OECD TG 414 study showed only mild effects which were not adverse, and did not demonstrate severe suffering.

In your comments, you also extrapolate the results of the OECD TG 414 study and estimate that higher dose levels of 750 and 1000 mg/kg bw/day would result in 21% and 28% higher relative liver weights, respectively. ECHA notes that this would be very close to the 'tolerable liver weight increase of ca 25%' which you present in your dose level setting rationale.

Finally, you consider that repeating the OECD TG 414 study with higher dose levels would not lead to a different conclusion on the hazard assessment.

ECHA notes that currently no conclusion on classification and labelling for developmental toxicity in accordance with the CLP Regulation can be made due to too low dose level selection, as adverse effects on the tested parameters at higher doses cannot be excluded. Thereby the study is inconclusive for hazard assessment.

*Conclusions*

Taken together your considerations on dose level selection (absence of effects in the DRF, lack of explanation on the inter-species extrapolation) and the results of the main OECD TG 414 study, ECHA considers that the dose levels in the main OECD TG 414 study were not selected according to the principles of EU Test Method B.31, OECD TG 414, i.e. with "*the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering*".

ECHA further notes that the original decision requested you to provide a study according to the OECD TG 414. As explained above, ECHA considers that the doses on the main OECD TG 414 study were not selected according to the principles of EU Test Method B.31, OECD TG 414, and therefore the provided study is not valid.

As detailed above, the request in the original decision was not met, and you are still required to provide a pre-natal developmental toxicity study in rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance subject to the present decision and conforming to the dose selection principles of test guideline OECD 414.

## Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

### A. 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[3].

### B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

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 variation in compositions reported by all members of the joint submission,
   - 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 and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

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

**Appendix C: Procedure**

The Substance is listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2017.

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 10 October 2016 ("the original decision"). Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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 27 January 2021.

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 adopted the decision under Article 51(3) of REACH.

**Appendix D: List of references - ECHA Guidance[5] and other supporting documents**

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 where relevant.

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 where relevant.

Read-across assessment framework (RAAF, March 2017)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[7]

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

**Appendix E: Addressees of this decision and the corresponding information requirements applicable to them**

You must provide the information requested in this decision for all REACH Annexes applicable to you.

| 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.