Helsinki, 21 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114367121-59-01/F
Substance name: L-P-MENTHA-1(6),8-DIEN-2-ONE
EC number: 229-352-5
CAS number: 6485-40-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/03/2013
Registered tonnage band: 100-1000

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

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **28 January 2019**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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 Kevin Pollard, Head of Unit, Evaluation E1

[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

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

"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.

You have sought to adapt this information requirement according to Annex VIII, Section 8.7.1., column 2 of the REACH Regulation, indicating that a pre-natal developmental toxicity study according to OECD TG 414 is available for an analogous source substance (read-across). However, by as explained below in Section 2, your read-across adaptation is rejected.

Therefore, your adaptation of the information requirement 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, 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.

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 especially the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to ECHA's end point specific guidance document[2].

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

A "pre-natal developmental toxicity study" (test method EU B.31./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 a study record for a pre-natal developmental toxicity study (OECD TG 414) with the analogue substance 5-isopropenyl-2-methylcyclohex-2-en-1-one (D-Carvone, EC 218-827-2, the source substance). However, the proposed read-across adaptation is inadequate to predict the properties of the registered substance subject to the present decision (L-Carvone (EC 229-352-5), the target substance), as explained below.

Furthermore, the provided robust study summary is inadequate for independent assessment within the meaning of Article 3(28) of the REACH Regulation defining the robust study summary (see ECHA's practical guide 3, version 2.0, Nov. 2012, *How to report robust study summaries*), as the level of detail in the description of the test material, the study design, and the reported results is not sufficient. More specifically, an independent assessment is only possible on all effects being reported, in addition or instead of interpreted results ("*No toxicologically relevant effect*" reported for all entries in Table 1). Additionally, you did not explain why the highest dose was limited to 200 mg/kg bw/d, which is neither a guideline-conforming limit dose, nor does it correspond to a (maternal) NOAEL extrapolated from existing studies with repeated exposure (375 mg/kg bw/d for 90 days) to the exposure duration of a pre-natal developmental toxicity study (>1000 mg/kg bw/d for <20 days).

Description of the grouping and read-across approach

In the technical dossier, you provide as read-across hypothesis under the endpoint 8.7.2: "*L-Carvone and D-Carvone, as enantiomers, are structurally similar compounds with the same molecular weight and molecular formula. The only structural difference is the opposite specific rotation. For example, the chirality is known to influence what olfactory receptors that L- and D-carvone interact with giving different odours/tastes. However, based on the available data, there is no information indicating that one of the isomers is clearly more toxic than the other (see 5. Data matrix).*"

Support of the grouping and read-across approach

[2] ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance Version 6.0, July 2017, R.7.6.2.3.2, p 486.

In the technical dossier, you provide that *"No data on the reproductive toxicity of L-Carvone is available. The enantiomer D-Carvone has a NOAEL of 200 mg/kg bw/day in a rat teratogenicity study (OECD 414; Carvone CLH report, 2012). There were no toxicologically relevant effects noted in maternal or fetal parameters in the D-carvone study. L-Carvone is predicted to have a comparable level of developmental toxicity to D-Carvone, so using a read-across approach, a NOAEL of 200 mg/kg bw/day is predicted for L-carvone. In addition, published toxicokinetic data demonstrates that L- and D-Carvone have no differences in metabolism, which further supports the read-across application ([redacted] 2001). On the basis of the metabolism and other toxicological properties (see 5. Data matrix), the information from the source chemical is reliable and read across from D-carvone to L-Carvone for developmental toxicity is proposed."*

ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, Section 1.5., and conclusion

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible

ECHA observes that, with regard to the sense of smell, you have identified the stereochemical differences of the source and target substance, which result in spacial differences and consequently, potential differences in receptor binding. However, ECHA notes that you did not address the toxicological relevance of this aspect with regard to developmental toxicity, when the rapidly developing embryo and fetus can be affected by binding of substances to continuously changing receptors resulting in developmental disorders.

In this regard, ECHA considers that particular attention needs to be given to the applicability of read-across for the endpoint of pre-natal developmental toxicity, since differences of stereochemically different teratogens are well documented (Smith SW, in Toxicol Sci (2009) 110 (1): 4-30). More specifically, as explained above, this feature of chiral substances does not allow read-across predictions in extrapolation of existing data on the stereoisomer, since receptor binding cannot be predicted from the geometrically different stereoisomer. Since many enantiomers of chiral teratogens are non-teratogenic, an absence of teratogenicity in the case of the analogous source substance D-Carvone is insufficient to conclude on the teratogenic potential of the target substance L-Carvone.

Therefore, ECHA concludes that the read-across based on studies conducted with the stereoisomeric analogue source substance D-Carvone (EC 218-827-2) does not allow to predict the properties of the target substance L-Carvone (EC 229-352-5) with regard to pre-natal developmental toxicity. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, section 1.5.Therefore, your adaptation of the information requirement 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 method EU B.31./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 5.0, December 2016) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, 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: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

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 22 February 2017.

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 did not receive any comments by the end of the commenting period.

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 relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 by each registrant.

If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally 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.