EUROPEAN CHEMICALS AGENCY

Helsinki, 10 October 2016

Addressee: [redacted]

Decision number: CCH-D-2114341495-48-01/F
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
List number: 915-730-3
CAS RN: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 13.07.2015
Registered tonnage band: 1000 or more tonnes per year

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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

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

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
    - **Ten weeks premating exposure duration for the parental (P0) generation;**
    - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
    - **Cohort 1A (Reproductive toxicity);**
    - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**
    - **Cohorts 2A and 2B (Developmental neurotoxicity).**

You are required to submit the requested information in an updated registration dossier by **17 April 2020** except for the information requested under point [1] for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **17 October 2017**. You may only commence the extended one-generation reproductive toxicity study as requested under point [3] after **17 January 2018**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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 Ofelia Bercaru, Head of Unit, Evaluation E3

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH 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 not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

In the technical dossier you have provided a study record for a repeated dose 28-day oral toxicity study in rats with the registered substance according to OECD TG 407. However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days, the number of animals per dose group is significantly lower and hence the statistical power of the test is lower. ECHA considers that these are both key parameters of the 90-day study which are not satisfied by the results of a 28-day study.

In the technical dossier you also stated that "*a 90-day repeated dose toxicity study can be waived because NTP has carried out a 13-week dermal toxicity study and the results will be included in an update of the REACH dossier when these results become available. According to the NTP website the study is already completed and the first results are presented but a report has not been published yet [...]. The results have not yet been reviewed by the registrant.*" ECHA notes that no endpoint study record has been provided in the technical dossier for this NTP study. Furthermore, no study results have been published on the NTP website to date although the 13-week study (NTP Study ID C20307) has been marked as "completed" (see https://ntp.niehs.nih.gov/testing/status/agents/ts-m990091.html). According to the "Management Status Report" dated 19 November 2015 which was published by the NTP at http://ntp.niehs.nih.gov/testing/types/cartox/msr/msr.pdf, the post peer review of the technical reports is in progress. Because no endpoint study record in form of a robust study summary has been provided in the technical dossier, ECHA cannot assess whether this NTP study fulfils the standard information requirement according to Annex IX, Section 8.6.2. Therefore, your statement cannot be accepted to fulfil this information requirement. In accordance with the REACH Regulation Annex IX, Section 8.6.2, the information on sub-chronic toxicity should have already been included in the registration dossier.

Furthermore, ECHA notes that the NTP study is performed by the dermal route which is not the most appropriate route of administration (see below), and the NTP study would fail to meet the information requirement for this reason. In addition, ECHA notes that the NTP study has been carried out using the test substance named 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (CAS RN 54464-57-2, EC number 259-174-3) whereas the registered substance is 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).

ECHA notes that the substance tested in the NTP study (one compound) is different from the registered substance (i.e. a reaction mass which contains the compound tested in the NTP study), and that in Appendix 1, Section 3(b) of this decision ECHA considers that the compound 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (CAS RN 54464-57-2, EC number 259-174-3) is structurally analogous to the registered substance, i.e. that there is structural similarity. However, no explanation has been provided to justify the read-across from a different substance to the registered substance, which is required according to Annex XI, 1.5. The failure to provide adequate and reliable documentation for this read-across and hence to meet the requirements of Annex XI, 1.5, are also additional reasons why this adaptation cannot be accepted. Thus ECHA concludes that the proposed adaptation based on the NTP study does not meet the information requirement for the reasons set out above.

As explained here 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.

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 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration for the following reasons:

- With respect to inhalation exposure, ECHA notes that the registered substance has a vapour pressure of 0.233 Pa at 23 °C and is classified as Skin Irrit. 2/ H315 (causes skin irritation). The provided information indicates that human exposure to the registered substance by inhalation is likely (e.g. PROCs 7 and 11: Industrial and non industrial spraying, respectively) and that the inhalation route is an appropriate route of administration. However, the exposure concentrations reported in the chemical safety report for inhalation is low (maximum [redacted] mg/m^3), and the overall concern for this route is not high. ECHA therefore considers that the inhalation route is not the most appropriate route of administration.

- With respect to dermal exposure, ECHA notes that significant absorption (corrected [redacted]%) was observed in the in vitro skin absorption study, and that the conditions of column 2 of Annex IX, 8.6.2 are met such that the dermal route is an appropriate route of administration.

- With respect to the most appropriate route of exposure, ECHA considered the following. Some systemic effects were observed after oral exposure in the provided study according to OECD TG 407 indicating that the registered substance causes systemic toxicity after oral administration by gavage. No toxicity was observed in the provided acute oral or dermal toxicity study in rats according to OECD TG 401 and 402, respectively. Thus, it is not clear that it is possible to obtain sufficient systemic availability after dermal exposure to evaluate the hazard properties of the substance, while it is clear that the oral route will enable evaluation of the hazard properties of the substance. Additionally, the oral route is the preferred route, as indicated in ECHA's guidance, for reasons associated with unnecessary distress (e.g. irritation at site of application), ease of dosing and greater systemic availability, and these reasons apply in this case also. For all these reasons, ECHA considers that the oral route is the most appropriate route of administration.

Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./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: Sub-chronic toxicity study (09-day), oral route (test method: EU B.26./OECD TG 408) in rats.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You have sought to adapt this information requirement according to Annex IX, Section 8.7.2., column 2. You provided the following justification for the adaptation: "*A test for developmental toxicity with a second species can be waived according to Column 2 of Annex IX of 1907/2006/EC and the Guidance Document on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance, because:*

1) *The developmental toxicity study in rats ([redacted]) does not indicate the substance to cause developmental effects, and;*
2) *There are no indications that the substance may be reproductive toxic e.g. the 28-day repeated dose toxicity study ([redacted]) and;*

A study (including pilot study) in which the transfer across the placenta and into milk of rats during and after pregnancy following repeated oral administration was studied showed that the transfer of OTNE or its metabolites across the placenta was barely detectable, and no OTNE was present in milk ([redacted]). In these studies, no adverse effects on reproductive organs or tissues were observed, transfer of OTNE or its metabolites across the placenta was barely detectable, and no OTNE was presence in milk. In addition, all risk ratios for worker, consumer and Man exposed via the environment are well below 1 (Chapter 9) (reference to Commission regulation EC no 134/2009, section 3.2)."

However, ECHA notes that your adaptation does not apply as such at Annex X level because for Annex X, a pre-natal developmental toxicity study on a second species according to Annex X, Section 8.7.2. is a standard information requirement, in addition to a prenatal developmental toxicity study in a first species according to Annex IX, Section 8.7.2. In addition, your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7., column 2 and is not supported by the ECHA guidance Chapter R.7a as a valid adaptation as will be explained in more details below. In particular, ECHA emphasises that the pre-natal developmental toxicity study in a second species can be omitted, if, taking into account the outcome of the first test and all other relevant available data, an adaptation according to Annex X, Section 8.7, column 2 or Annex XI can be justified. Currently, no such justification is given in the dossier.

Specifically, ECHA notes that the developmental study in rats is a study in a first species and does not provide an adaptation for the prenatal developmental toxicity study in a second species, according to Annex X, 8.7., column 2. ECHA notes that the absence of "indications that the substance may be reproductive toxic e.g. the 28-day repeated dose toxicity study ([redacted])" is not a valid adaptation according to Annex X, 8.7., column 2 or Annex XI. With respect to the provided study report for [redacted], ECHA notes your statement that for the registered substance "*minimal transfer across the placenta*" was observed. However, it is emphasised that even small quantities of substance can exert developmental effects and, therefore, "*minimal transfer across the placenta*" cannot by itself support the assumption of absence of developmental effects. ECHA also emphasises that this study was conducted in rats and that placenta varies between different species. Therefore, showing minimal transfer across the placenta in rats is not by itself indicative of minimal transfer across the placenta in rabbits or other species. Thus this argument also is not a valid adaptation according to Annex X, Section 8.7., column 2 or Annex XI.

The argument you provided regarding risks ratios for worker, consumer and man via environment are not a valid adaptation according to column 2 of Annex X, 8.7. or according to Annex XI.

Additionally, ECHA considers that you have not explained why all of your arguments, when viewed together, provide a sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the registered substance has not a particular dangerous property in the context of prenatal developmental toxicity, and that therefore there is a failure to provide adequate and reliable documentation according to Annex XI, 1.2. For this reason, and the reasons already presented above, ECHA considers that, as required by the adaptation in Annex XI, Section 1.2 of the REACH Regulation, all your arguments together do not provide sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the registered substance has not a particular dangerous property in the context of prenatal developmental toxicity in a second species. ECHA therefore considers that the proposed adaptation fails to meet the requirements of Annex XI, 1.2.

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.

The test in the first species was carried out by using a rodent species (rats). According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid with low vapour pressure of 0.233 Pa at 23 degC, 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 second species (rabbits) by the oral route.

3. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement. While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex X, Section 8.7., column 2 and Annex XI, Section 1.2. You provided the following information: "*A two-generation reproduction study can be waived because in the Guidance Document on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance is indicated that the study does not need to performed, because*

1) *The developmental toxicity study in rats does not indicate the substance to cause developmental effects ([redacted]);*
2) *There are no indications that the substance may be reproductive toxic e.g. the 28-day repeated dose toxicity study ([redacted]) and;*
3) *A study (including pilot study) in which the transfer across the placenta and into milk of rats during and after pregnancy following repeated oral administration was studied showed that the transfer of OTNE or its metabolites across the placenta was barely detectable, and no OTNE was presence in milk ([redacted]).*

No adverse effects on reproductive organs or tissues were observed and therefore a two generation study is not needed. In addition, all risk ratios for worker, consumer and Man exposed via the environment are well below 1 (Chapter 9) (reference to Commission regulation EC no 134/2009, section 3.2). When the results if the 90-day repeated dose dermal toxicity study from the NTP become available, the need for reproductive toxicity testing will be re-evaluated."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7., column 2, because an extended one-generation reproductive toxicity study is an information requirement at Annex X level, even though available repeated dose toxicity studies indicate no adverse effects on reproductive organs or tissues or do not reveal other concerns in relation with reproductive toxicity.

Furthermore, it is not possible to assume/conclude based on the provided information if the registered substance has not a dangerous (hazardous) property on sexual function and fertility, according to the provisions of Annex XI, 1.2. In particular, information on the following relevant aspects in relation to sexual function and fertility have not been covered: The repeated dose 28-day oral toxicity study in rats (OECD TG 407) provides information on histopathological changes of reproductive organs for the first generation with limited statistical power but does not provide information on functional fertility or other aspects of reproductive toxicity and information from the pre-natal developmental toxicity study (OECD TG 414) in rats regarding sexual function and fertility is limited to the maintenance of the pregnancy from implantation up to close to the parturition. In addition, you did not provide information on hazardous properties due to pre/peri/postnatal exposure manifested during the postnatal development including sexual maturation and histopathological integrity of the reproductive organs at adulthood. With respect to the provided study report for [redacted], ECHA notes your statement that for the registered substance "*minimal transfer across the placenta*" was observed. However, it is emphasised that even small quantities of substance can exert effects on reproductive toxicity, e.g. on sexual function and fertility in offspring and, therefore, "*minimal transfer across the placenta*" cannot by itself support the assumption of absence of such effects. Thus, the information from these studies, individually and in aggregate, do not allow to assume/conclude that the substance has not hazardous properties with regard to sexual function and fertility and consequently REACH Annex XI, Section 1.2 requirements are not met. Furthermore, the criteria of Annex X, Section 8.7.3., column 2 are met for inclusion of Cohorts 2A and 2B (developmental neurotoxicity) as explained below and information for those properties is not provided.

The argument you provided regarding risks ratios for worker, consumer and man via environment are not a valid adaptation according to column 2 of Annex X, 8.7. or according to Annex XI.

Additionally, ECHA considers that you have not explained why all of your arguments, when viewed together, provide a sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the registered substance has not a particular dangerous property in the context of the extended one generation reproductive toxicity study, and that therefore there is a failure to provide adequate and reliable documentation according to Annex XI, 1.2.

For this reason, and the reasons already presented above, ECHA considers that, as required by the adaptation in Annex XI, Section 1.2 of the REACH Regulation, all your arguments together do not provide sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the registered substance has not a particular dangerous property in the context of extended one generation reproductive toxicity study. ECHA therefore considers that the proposed adaptation fails to meet the requirements of Annex XI, 1.2.

ECHA concludes that your adaptation of the information requirement is therefore rejected.

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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). Ten weeks exposure duration is supported also by the lipophilicity of the substance (logK_{OW} = 5.65 at 30°C) to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

It is recommended that results from a range-finding study (or range finding studies) for the extended one-generation reproductive toxicity study are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that existing information on a substance (acetyl ethyl tetramethyl tetralin, CAS RN 88-29-9, AETT) structurally analogous to the registered substance derived from available *in vivo* studies show evidence of structural and functional neurotoxicity.

The substance acetyl ethyl tetramethyl tetralin (CAS RN 88-29-9, AETT) is a structural analogue to 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (CAS RN 54464-57-2) according to the corresponding "Review of Toxicological Literature" published by the NTP.[2] Because 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone is the main constituent of the registered substance, ECHA considers that AETT can be considered as a structural analogous substance to the registered substance within the meaning of column 2, Section 8.7.2 of Annex X even if it would not fulfil the conditions of Annex XI, Section 1.5 concerning the read-across.

This review states that "*AETT is neurotoxic in animals (Eiermann, 1980). Topical administration (dose n.p.) produced demyelination in rats (Spencer et al., 1978a, b). Repeated exposure to AETT (dose n.p.) produced hyperirritability and limb weakness in rats. The brain, spinal cord, and peripheral nerves showed progressive neuronal ceroid degeneration and myelin bubbling* [redacted] *In Sprague-Dawley rats fed ~50 mg/kg/day of AETT dissolved in ethanol, myelin was damaged, but Schwann cell somal functions were not significantly affected (Sterman and Spencer, 1981). Percutaneous administration of high doses (n.p.) to rats caused a gait abnormality that became severe ataxia. Microscopically, significant cerebellar changes and widespread accumulation of ceroid-like pigmentation in the neuronal cytoplasm were seen* [redacted]*. In Wistar rats, i.p. administration of AETT (dose n.p.) for three months produced a significant increase in neuronal ceroid lipofuscin and a significant impairment of learning ability* [redacted]."

ECHA therefore concluded that the neurotoxic properties of the structurally analogous substance AETT suggests similar neurotoxic effects and/or neurotoxic mechanism/mode of action for the registered substance meeting the criteria for a particular concern for developmental neurotoxicity as stated in Annex X, Section 8.7.3 column 2 paragraph 2 sixth indent of the REACH Regulation.

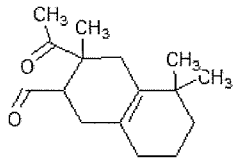
In your comments to the draft decision, you explain that the neurotoxic effects observed for the structural analogue AETT result from the formation of its gamma-diketone metabolite, a well-known group of neurotoxicants. ECHA notes that scientific evidence supports that gamma-diketones are neurotoxic. According to your explanation, the formation of a diketone metabolite is not possible for the registered substance because it bears a methyl instead of an ethyl group in the relevant position of the molecule, and preliminary tabular results on the individual animals of an NTP study on 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone do not mention neurotoxic effects.[3] Furthermore, as supporting information, you refer to the substances AHTN (tonalid) and AHDI (phantolid) which also bear a methyl instead of an ethyl group in the relevant position. You state that AHTN and AHDI do not cause neurotoxicity [redacted] and, therefore, there would be no concern for developmental neurotoxicity anticipated for the registered substance.

ECHA notes that there are differences between the structure of 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone and AHTN or AHDI which affect the metabolisms and reactivity and, thus, may also affect the neurotoxicity. In particular, the additional methyl group in position 2 of the ring structure changes the electron distribution, spatial orientation and further the function of the ethanone and position 3 methyl group.
You consider that the lack of the aromatic ring and the quaternary carbon would reduce the

[2] See http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/isoesuper_508.pdf

[3] See http://ntpsearch.niehs.nih.gov/texis/search/?query=54464-57-2&pr=ntp_web_entire_site_all&mu=Entire+NTP+Site

reactivity, but you do not substantiate this with data. However, due to these structural differences, information on neurotoxicity from AHTN and AHDI, if available, would not reduce the concern for potential developmental neurotoxicity of the registered substance. The registered substance might e.g. form a metabolite which bears an aldehyde and ketone function in the relevant positions as shown in your response (metabolite no 6):



ECHA further notes that the aldehyde and ketone functions of this metabolite could react in a similar way with primary amines as gamma-diketones or via other modes of action and cause the neurotoxicity. Aldehydes and ketones can selectively react with amines. In particular, it should be emphasised that the aldehyde function is typically more reactive towards nucleophiles than the ketone function because more alkyl groups reduce the reactivity of the carbonyl carbon due to an electron releasing and a steric effect. Thus, an aldehyde with only one alkyl group is more reactive than a ketone with two alkyl groups and such metabolites could similarly contribute to the neurotoxicity. Based on these considerations the concern for (developmental) neurotoxicity based on information on AETT remains although the assumed reactive groups are not exactly the same.

Furthermore, in your comments to the draft decision you stated that: "In addition, OTNE has not shown any sign of neurotoxicity during the 28-day oral repeated dose toxicity (OECD TG 407), the dermal 13-weeks repeated dose toxicity (NTP study similar to OECD TG 411, a summary of which is included as Appendix 1) and the developmental toxicity study (similar to OECD TG 414)." ECHA notes that these studies do not investigate developmental neurotoxicity (ECHA guidance on Information Requirement and Chemical Safety Assessment, Chapter R.7a, Reproductive toxicity, version 4.1, October 2015: "*Cohorts 2A and 2B provide information on developmental neurotoxicity and Cohort 3 on developmental immunotoxicity; this information is not covered by any other study within REACH requirements*"). In this case, the concern for developmental neurotoxicity stems from information on a structural analogue of one component of the registered substance and not from the existing information on repeated dose toxicity studies for the registered substance. The information from existing studies is not comprehensive enough to conclude on the repeated dose toxicity or neurotoxicity of the registered substance and an oral sub-chronic toxicity study is required in section 1.

ECHA notes that the preliminary tabular results of the dermal NTP study (ID C20307, see also section 1) using one component of the reaction mass of the registered substance, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone, are very limited and do not mention any details with respect to study results/ outcome. ECHA notes that the tabular results are a mere classification of investigated organs/ tissues as "normal" or "with observations". The observed effects are only mentioned without further qualification or quantification (e.g. "skin inflammation"). It seems that other observations (e.g. behavioural observations) are not recorded in these tabular summaries and the completeness of these records cannot be established. Therefore, ECHA is of the view that these preliminary records do not provide conclusive evidence on whether the examined substance has or has not a neurotoxic property.

Additionally, ECHA notes that the substance used in this dermal NTP study is 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone is the main constituent of the registered substance but not the registered substance itself. Hence, ECHA considers that it cannot be concluded from this information either whether the other constituents of the registered substance are neurotoxic or not.

With respect to the supporting information on AHTN (Tonalid) and AHDI (Phantolid), ECHA notes that the information provided in your comments to the draft decision is not sufficient to conclude whether they indeed lack neurotoxic potential (in addition, the referenced article and/or details on the study and its results were not provided). ECHA also notes that there is a 90-day oral study available with AHTN conducted to up to 50 mg/kg bw/day dose levels but neurobehaviour was not examined (see ECHA dissemination site, unnamed study, 1996; http://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/12034/7/6/2). Thus, the absence of neurotoxicity from AHTN (and AHDI) cannot be independently confirmed on the basis of the above referred studies.

Therefore, ECHA concludes that the information provided as part of your comments does not exclude the particular concern on (developmental) neurotoxicity arising from the existing information on the structurally analogous substance AETT.

As a result, the developmental neurotoxicity Cohorts 2A and 2B need to be included in the study because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* studies on a substance structurally analogous to the registered substance suggests similar neurotoxic effects and/or neurotoxic mechanism/mode of action for the registered substance.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid with low vapour pressure of 0.233 Pa at 23 °C, ECHA concludes that testing should be performed by the oral route.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohorts 2A and 2B (Developmental neurotoxicity).

Currently, no triggers for the extension of Cohort 1B and the inclusion Cohort 3 (developmental immunotoxicity) have been identified based on the available information. However, the sub-chronic toxicity study (90-day) requested in this decision (request [1]) and/ or any other relevant available information, including information which has become available since the point in time when the sub-chronic toxicity study (90-day) was requested, may provide information that could trigger such changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **17 October 2017**. In such update you may also include your considerations whether in light of these results and/ or other available information if changes in the study design are needed. If ECHA identifies a need for changes to the study design, it will inform you by **17 January 2018** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **17 January 2018**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study which results will need to be submitted by **17 April 2020** covering all requests.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you may also include in the registration update your considerations whether changes in the study design are needed because new information shows that the triggers for expanding the study as described in column 2 of Section 8.7.3. are met (see also ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.1, October 2015)). Furthermore, in cases where you have already commenced the study in accordance with this decision, you may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study.

The justification for the changes in the study design must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

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 30 November 2015.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

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) and the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.
ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA 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 during its MSC-48 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2017.

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

3. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.