EUROPEAN CHEMICALS AGENCY

Helsinki, 8 January 2018

Addressee: [redacted]

Decision number: CCH-D-2114384240-56-01/F
Substance name: Reaction mass of Bis(1,2,2,6,6-pentamethyl-4-piperidyl) sebacate and Methyl 1,2,2,6,6-pentamethyl-4-piperidyl sebacate
EC number: 915-687-0
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23.10.2015
Registered tonnage band: >1000T

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 IX, Section 8.7.2; test method: EU B.31/OECD TG 414) in a first species (rats or rabbits), oral route with the registered substance;**

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

4. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3; test method: 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).**

5. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance including each relevant constituent present in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable;**

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.

You are required to submit the requested information in an updated registration dossier by ***15 July 2021*** 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 **15 January 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 4 after **15 April 2019**, 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.

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

Grouping of substances and read-across approach

In the registration, you have adapted the standard information requirement for an:

- Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2);
- Pre-natal developmental toxicity (Annexes IX and X, Section 8.7.2); and
- Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

A. Description of the grouping and read-across approach proposed by the Registrant

You propose to predict properties of the target (registered) substance Reaction mass of Bis(1,2,2,6,6-pentamethyl-4-piperidyl) sebacate and Methyl 1,2,2,6,6-pentamethyl-4-piperidyl sebacate (EC No.: 915-687-0; hereafter referred to as Tinuvin 292) on the basis of results obtained with the source substance Bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate (CAS No. 52829-07-9; hereafter referred to as Tinuvin 770).

You have provided the following reasoning: "*The physico-chemical properties of Tinuvin 770 are in good correlation with the data for the substance under evaluation. Specifically, the water solubility was found to be in a comparable (low) range as is the partition coefficient. This relationship gives rise to an expected comparable degree of bioavailability and toxicological profile. On this basis, it is expected that any toxicological effects shown by the reference substances should encompass the full range of potential toxicological properties and furthermore might even overestimate any similar effects of the notifiable substances.*".

ECHA understands this as the hypothesis under which you make predictions for the properties listed above.

B. Information submitted by the Registrant to support of the grouping approach and read-across hypothesis

You have provided a read-across justification as a separate attachment in the IUCLID, section 13. In summary you provide the following arguments to support the read-across approach:

- The target substance (Tinuvin 292) is a multi-constituent substance consisting of [redacted]. The source substance (Tinuvin 770) is a mono-constituent substance. The proposed source substance (Tinuvin 770) differs from the major constituent of the target substance in that it has one methyl- group less on the [redacted]-moeties. Both of the ester-bonds in source and target substances are assumed to be hydrolysed. As result the hydrolysis products sebacic acid and pentamethylpiperidinol are formed from the target substance (Tinuvin 770). The hydrolysis products of the source substance (Tinvin 292) are the products sebacic acid, tetramethylpiperidinol, and methanol;

- Theoretical considerations on toxicokinetics: "The degradation comprehensively studied and described above in an abiotic hydrolysis test may display the primary metabolic pathway, followed by Phase II reactions and elimination steps. The parent substances may be absorbed to some extent, but might face some withholding due to the size of the molecule. However, the degree of gastro-intestinal hydrolysis may govern predominantly absorption and bioavailability of the cleavage products. It could be shown that piperidinols are the predominant breakdown products which only differ in the absence or presence of the methyl-group attached to the nitrogen. The N-methylated piperidinol originating from Tinuvin 292, might undergo N-demethylation, finally leading to HTMP, the same compound as is formed by Tinuvin 770 metabolism."; and

- The toxicity profile of the source (Tinuvin 770) and target (Tinuvin 294) substances are discussed for the toxicity endpoints where data are available on both substances: *Acute toxicity* – both source (Tinuvin 770) and target (Tinuvin 294) substances have low acute toxicity; *Skin/eye irritation* - source substance (Tinuvin 770) is not irritant to the skin but irritant to the eye whereas the target substance (Tinuvin 294) is not irritant to the skin or eye; *Skin sensitization* - source substance (Tinuvin 770) is not irritant to the skin sensitizer whereas the target substance (Tinuvin 294) is a skin sensitizer; and *Genetic toxicity* – both substances were negative in the Ames test and source substance (Tinuvin 770) was not clastogenic, whereas target substance (Tinuvin 294) was clastogenic in the *in vitro* test.

  You provided comments to the draft decision of the registered substance Tinuvin 292 on 15 January 2016. ECHA notes that on 20 December 2016 you provided comments on the draft decision of the proposed source substance Tinuvin 770 (CCH-D-2114346831-49-01/D). In these comments, you state the following: *"Since both compounds are very similar in structure and toxicological properties, a read across approach has been proposed and an updated read across justification document has been submitted as part of the comments to the draft decision for Tinuvin 292.*

The registrant believes that both compounds should be evaluated together and the remaining data gaps should be addressed by a testing strategy aligned according to the proposed read across approach, thereby reducing the amount of laboratory animals required".

ECHA agrees that it is beneficial to perform the evaluation of both substances together. As the comments on the source substance were received at a later stage they are considered to represent the latest opinion of the Registrant on how to address the identified data gaps and thus ECHA has exceptionally based the analysis on these comments.

You have provided the following studies that provide information on repeated dose toxicity:

i. Experimental result on the registered substance; Reliability 1 (reliable without restrictions); 2010; GLP; Repeated Dose 28-Day Oral Toxicity in Rodents (according to OECD TG 407) conducted in rats via the oral route with the target (registered) substance (Tinuvin 294); The following doses were used: 0, 100, 3000, 750/1000 (male/female) mg/kg/day; Your conclusion on the results: Adverse findings were confined to the high-dose group where mydriasis (dilation of the pupil) at dose levels of 750/1000 mg/kg/day (males/females);

ii. Read-across from supporting substance (structural analogue or surrogate); Reliability 2 (reliable with restrictions); 1974; non-GLP; non-Guideline (Principle of the test: similar to OECD TG 408; Reported deviations: "*stability and homogeneity of the test substance formulation was not determined*", "No functional observations performed", "*No haematology, clinical chemistry and urinalysis in intermediate dose groups*", "*Slight deviations in biochemistry, macroscopic and histopathological examinations*", and "*Inflammation observed in all animals, including control group*") conducted in rats via the oral route (feed) with the source substance (Tinuvin 770); The following doses were used: 0, 400, 1300 and 4000 ppm (corresponding to 26/29, 80/90, 261/277 mg/kg/day – M/F); Your conclusion on the results: "*At macroscopic or histopathological examination no treatment-related abnormalities were noted. The NOAEL was not established. The LOAEL was determined at 29 mg/kg bw based on the decreased body weight gain in females.*";

iii. Read-across from supporting substance (structural analogue or surrogate); Reliability 1 (reliable without restrictions); 2007; GLP; One-Generation Reproduction Toxicity Study Guideline (according to OECD TG 415) conducted in rats via the oral route (gavage) with the source substance (Tinuvin 770); The following doses were used: 0, 3, 30, 300 mg/kg/day,;Your conclusion on the results: "*Based on the results, the parental No Observed Adverse Effect Levels (NOAEL) were established at 30 mg/kg/day based on decreased body weights, body weight gain and food consumption of males and females. The NOAEL for developmental toxicity was set at 30 mg/kg bw based on reduced pup weight during lactation, but not associated with any other developmental adverse effect. The NOAEL for reproductive toxicity was set at >= 300 mg/kg/day based on the absence of effects.*"; *and*

iv. The read-across justification lists what appears to be a sub-acute study conducted with the proposed source substance (Tinuvin 770) study also cited in the dose setting rational for the one-generation reproduction toxicity study *"160 albino rats of theCFY strain, 20 male and 20 female per dose group were dosed by gavage with 0, 50, 200 and 600 mg/kg bw for 4 weeks. The NOEL was found to be 50 mg/kg/day. Reaction to treatment were at 600 mg/kg/day reduced grooming activity, salivation and death of two females as well as reduced rate of bw gain, and at 200 mg/kg/day slightly reduced rate of bw gain."*

v. In your comments to the draft decision you have provided a summary of the toxicological data on the metabolites:

- HTMP: acute and genetic toxicity, skin irritation and sensitisation, combined repeated dose and reproductive/development toxicity screening test;
- HPMP: acute toxicity, skin and eye irritation, skin sensitisation and Ames test;
- Sebacic acid: acute toxicity, skin irritation and sensitisation, Ames test, repeated dose toxicity, developmental toxicity.

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

With regard to the proposed predictions ECHA has the following observations:

(i) Substance characterisation of source and target substances

The substance characterisation of the source substance(s) need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 *"How to report on Read-Across"* it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

You have provided the following statement with regard to the impurity profile of the source and target substances: *"None of the potential impurities is considered to be of toxicological concern in the amounts they occur in the product"*. However, no impurities have been reported for the source substance (Tinuvin 770).

Currently the source substance and impurity profile cannot be assessed using the information provided in the registration dossier and the suitability of the substances for read-across purposes cannot be verified. Therefore ECHA cannot reach a conclusion whether the source substances can be used to predict properties for the registered substance.

In your comments to the draft decision you have provided additional information on the composition of the source substance, including new information on impurities marked as confidential. ECHA considers that this information allows an assessment of the suitability of the source substance for read across purposes. ECHA concludes that the impurity profiles of the source and target substances are not likely to have an impact on the proposed read-across approach.

(ii) Explanation on why and how the structural similarities allow predictions

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.

You argue in your read-across justification that prediction from the source substance to the target substance is possible because the physico-chemical properties of the target substances resemble those of the source substance, the ADME characteristics are expected to be similar, and the substances share the same mechanism for break down.

ECHA notes that the source and target substances are similar in terms of the 'sebacate' moeity. However, the substances also display structural differences: the piperidinols in the target substance are 'N-methyl' *v.* 'N-H' in the source substance. In addition, the target substance is a multi-constituent substance consisting of Bis(1,2,2,6,6,-pentamethyl-4-piperidyl)sebacate and methyl 1,2,2,6,6,-pentamethyl-4-piperidylsebacate whereas the source substance is a mono-constituent substance consisting of Bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate.

You assume that both substances undergo hydrolysis. If both ester functions are fully hydrolysed sebatic acid, pentamethylpiperidinol and methanol (in the approximate ratio of ~4.5:~8.1:1) will be formed from the target substance. In contrast, if the source substance is fully hydrolysed sebatic acid and tetramethylpiperidinol will be formed (in the ratio of 1:2). ECHA notes that you have not provided any explanation as to why prediction is possible despite the fact that different substances are formed after hydrolysis. In addition, different mono-esters are formed as intermediates during the hydrolysis. You have not provided any information on how these structural differences may impact the toxicity of the substances and thus affect the possibility to predict the properties of the target substance from the data of the source substance.

ECHA concludes that you have not addressed the obvious structural differences between the source substance and the target substance and did not explain why those differences would not lead to differences in the toxicity profile of target and source substances. The provided explanation is not considered as valid to establish a scientific credible link between the structural similarity and the prediction.

In your comments to the draft decision you have provided new information on the toxicokinetic behaviour of the registered and source substance and you have provided toxicological data on the hydrolysis products of these substances. You further explain the common structural elements of the target and source substances and outline the structural differences. You also explain a possible common mechanism of action for systemic toxicity, i.e. interaction with the neurotransmitter system mediated via inhibition of the acetylcholine receptor and indicate that the piperidyl moiety may be the causative structural element.

ECHA notes that while there are still uncertainties regarding e.g. the rate of the hydrolysis reaction (see section v), toxicological data especially on metabolites, the updated read-across justification is considered as valid to establish a scientifically plausible link between

the structural similarity and the prediction for repeated dose toxicity, in particular in view of the similar toxicity profiles in repeated dose toxicity studies observed for Tinuvin 292, Tinuvin 770 and HTMP, the piperidyl moiety of Tinuvin 770 (see section iii).

Currently a plausible link between the structural similarities and the prediction for the properties investigated in PNDT studies and EOGRTS, however, is not established. You did not scientifically establish how relevant the mechanism of action identified in the repeated dose toxicity studies is to pre-, peri- and post-natal development and/or reproduction. In particular, it is not known whether the same or different mechanisms are acting on the developing fetus or at peri-and post-natal development and reproduction and at which doses for the source and target substances. ECHA concludes that currently there is not sufficient information to support the claim that the same type and similar strength of effects would be observed when source and target substance are administered in PNDT and EOGRTS studies.

(iii) Support of a similar or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

You have provided a data matrix that compares the available toxicological data on the target and source substances. However, you have merely asserted that the results can be read across, no explanation as to how and why the properties of the target substance can be predicted prediction from the source substance have been provided.

ECHA notes that the provided data matrix indicates that source and target substances are similar in terms of physicochemical properties, anaerobic hydrolysis, and acute toxicity.

With regard to systemic toxicity after repeated administration the following information is available:

(a) A sub-acute study (28-days; see section 0.2 point i.) with the (registered) target substance: Adverse finding – mydriasis (retarded adaptation of the pupil to light); LOAEL 750/1000 mg/kg/day (males/females). Additionally, increased food consumption was observed;
(b) A sub-acute study (28-days; see section 0.2 point iv.) with the source substance: Adverse findings – mortality at 600 mg/kg/day; NOEL 50 mg/kg/day;
(c) A sub-chronic study (90-days; see section 0.2 point ii. with the source substance: Adverse findings – decreased body weight and body weight gain in females LOAEL 29 mg/kg/day; and
(d) A one-generation study (duration 103-106 days in males and 55-63 days in females; see section 0.2 point iii.) with the source substance: Findings – decreased body weights, body weight gain and food consumption of males and females was observed at 300 mg/kg/day.

ECHA notes that the target and source substances differ with respect of the following properties: eye irritation (target substance is not irritating to the eye whereas the source substance is irritating to the eye), skin sensitisation (target substance is sensitising to the skin whereas the source substance is not sensitising to the skin) and genetic toxicity (target substance is clastogenic *in vitro* but not *in vivo* whereas the source substance is clastogenic *in vitro*). ECHA considers that effects observed in the available repeated dose toxicity studies suggest that the target and source substances differ also in their effects with regard to systemic toxicity. The target substance causes mydriasis but not reduced body weight. In contrast, the source substance consistently causes reduced body weight (mydriasis was not investigated; as there were no functional neurological investigations in the available studies).

ECHA concludes that the presented evidence in the data matrix does not support a similar or regular pattern of toxicity as a result of structural similarity. Therefore it cannot be verified that the analogue substance can be used to predict properties of the registered substance.

In your comments to the draft decision you have provided the following information:

- both substances cause ocular irritation, which is most likely due to hydrolysis products HPMP and HTMP. Differences in the potency of irritation may be due to physical state (Tinuvin 770 is solid whereas Tinuvin 292 is liquid) and/or due to different hydrolysis rates of the substances,

- both substances show a protein binding alert in the OECD toolbox. However, the difference in skin sensitisation potential may be due to different dermal absorption as Tinuvin 770 is solid whereas Tinuvin 292 is liquid, which absorbs easier than a solid material,

- *in vitro* chromosome aberration test gives false positive results in some cases. Therefore, the positive *in vitro* study with Tinuvin 292 was further investigated in an *in vivo* clastogenicity study. As the *in vivo* study was negative it can be concluded that both substances are non-genotoxic,

- detailed analysis of the repeated dose toxicity studies conducted with both substances. Both substances cause ptosis and mydriasis at high doses, and decreased body weight and body weight gain. You conclude that both substances have a similar toxicological profile.

- summary of the toxicological data on metabolites HTMP (hydrolysis product of Tinuvin 770), HPMP (hydrolysis product of Tinuvin 292), and sebacic acid (common metabolite formed from both substances). You conclude that sebacic acid is of low toxicity and that the toxicity of parent substances are "*very likely*" due to HPMP and HTMP moieties. You further state that although no repeated dose toxicity data is available for HPMP it is likely to cause similar effects as HTMP since "*mydriasis was also observed with Tinuvin 292 itself*". Regarding PipSeba and Tinuvin 770 Monoester (metabolites) you state that due to their structures (piperidinol moieties and carboxylic acid residues) "*these substances are most likely very similar to the parent compounds in regard of their toxicity*".

Based on the information provided in the comments, especially on assumed metabolites, ECHA considers that sufficient information has been provided to support the similar toxicological profile of the substances regarding repeated dose toxicity. Further, sufficient information has been provided to explain the differences, which ECHA has addressed above.

ECHA considers that there is not sufficient information to support the similar toxicological profile of the target and source substances regarding pre-natal developmental toxicity and extended one-generation reproductive toxicity, as , for example, bridging studies (such as screening study(ies) conducted with the target substance and/or the potential metabolite HPMP) are not available. Such studies would allow comparison of developmental/reproductive effects between the target and source substances. In the absence of such information, a similarity in toxicological profiles is not established and there is not an adequate basis for predicting the properties of the registered substance from the data (PNDT and EOGRTS studies) obtained with the source substance.

(iv) Reliability and adequacy of the source studies

Annex XI, Section 1.5 provides with regard to the reliability and adequacy of the source studies that in all cases the results of the read-across should:

- *be adequate for the purpose of classification and labelling and/or risk assessment;*
- *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);*
- *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter; and*
- *adequate and reliable documentation of the applied method shall be provided.*

Annex XI, Section 1.1.2 provides with regard to the use of existing data that data from experiments not carried out according to GLP or not conducted according to the test methods referred in Article 13(3) is considered equivalent to data generated by the test methods referred in Article 13(3) if the following conditions are met:

- *adequacy for the purpose of classification and labelling and/or risk assessment;*
- *adequate and reliable coverage of the key parameters forseen to be investigated in the corresponding test method referred to in Article 13(3),*
- *exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and*
- *adequate and reliable documentation of the study is provided.*

With regard to the requirement for a sub-chronic (90-day) toxicity study (Annex IX, Section 8.6.2.), ECHA makes the following observations: The source study provided in the technical dossier (see point ii. in section B above) was not conducted according to GLP and has numerous deficiencies when compared to the current OECD TG 408. The main missing key aspects/elements are analytical conformation on the stability of the test material; missing functional observations; and incomplete haematology, clinical chemistry and urinalysis. In addition, inflammation was observed in all animals in the study, including controls. The LOAEL (29 mg/kg/day) based on body weight derived from this study differs significantly from the the NOAEL (300 mg/kg/day; also based on body weight) derived in the OECD 415 study with the source substance despite the fact that the exposure duration is similar. ECHA considers that the inflammation may have compromised the reliability of the study. Therefore, given the deficiencies identified above, ECHA concludes that the source study does not provide the information required by Annex IX, Section 8.6.2., because it does not meet the requirements of Annex XI, Section 1.1.2. and Section 1.5.

ECHA understands that you have used a weight of evidence approach in the registration dossier of Tinuvin 770 to fulfil the information requirement for sub-chronic (90-day) toxicity. ECHA notes that all studies show similar effects (such as reduced body weight and body weight gain, and ptosis and mydriasis in high doses), and exposure duration in two of the studies is 90 days. Therefore, ECHA considers that despite the shortcomings observed in the individual studies, such as the sub-chronic (90-day) study described above, sufficient information from several studies has been provided to conclude on the hazard profile of Tinuvin 770.

With regard to the requirement for an extended one-generation study (Annex X, Section 8.7.3.), ECHA makes the following observations: The source study provided in the technical dossier (see point iii. in section B above) is a "One-generation reproduction toxicity study" according to OECD TG 415 and according to GLP. However, this study does not provide the information required by Annex X, Section 8.7.3., because it does not cover key parameters, exposure duration and life stages of an extended one-generation reproductive toxicity study. The main missing key aspect/element is an extensive postnatal evaluation of the F1 generation (OECD TG 443). Furthermore, the criteria of Annex X, Section 8.7.3., column 2 are met for inclusion of cohort 2A/2B (developmental neurotoxicity) and information for those properties is not provided. Therefore, given the deficiencies in coverage of the key parameters identified above, ECHA concludes that the source study does not provide the information required by Annex X, Section 8.7.3., because it does not meet the requirements of Annex XI, Section 1.5.

ECHA notes that in your comments to the draft decision of the registered substance (Tinuvin 292) you consider the one-generation reproductive toxicity study sufficient to fulfil the information requirement of reproductive toxicity (Annex X, 8.7.3). However, you do not address the deficiencies mentioned above and ECHA notes that in the comments to the draft decision of the source substance Tinuvin 770 you state that one-generation reproductive toxicity study "*may not be sufficient*" and you agree to conduct an extended one-generation reproductive toxicity study (OECD 443) with Tinuvin 770.

(v) Toxicokinetics

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source

and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

You state in your read-across justification that "*taking into consideration toxicokinetics and metabolism of the substances, there is a high probability that these substances behave similarly, e.g. are poorly absorbed as such. However, a metabolic step is likely to happen in the gastrointestinal tract by hydrolysis. Having established that the chemical functionalities of the substances are expected to be essentially identical, and that the difference are of minor concern compared to the similarities shown, it seems reasonable to consider the notifiable substances to be members of a kind of compound family.*".

ECHA notes that different but adverse effect(s) are observed for both the target and source substances. No data have been provided to support the claim of low bioavailablilty. ECHA considers that the adverse effects observed in available studies do not support a notion that the substances "*are poorly absorbed*".

In addition, ECHA notes that the target substance is a multi-constituent substance whereas the source substance is a mono-constituent substance. You have provided information on abiotic hydrolysis on both substances. This information indicates that the substances are stable at acidic conditions and hydrolyse above pH 9. However, this information is only indicative of what may happen *in vivo*. There is no toxicokinetics or metabolic information provided to support any claims with regard to rate and extent of metabolism in mammals.

Furthermore, ECHA notes that different mono-esters are formed when the target and source substances are hydrolised. No explanation has been provided to what extent this influences further metabolism of the respective mono-esters. Moreover, ECHA notes that the piperidinols formed differ between substances. No information has been provided on further metabolism of the different piperidinols (*i.e.* tetramethylpiperidinol from the source substance and pentamethylpiperidinol from the target substance).

Finally, ECHA notes that the hydrolysis will not be instantaneous, thus there will be simultaneous exposure of the test organism to the parent compounds as well as to the metabolites. No explanation has been provided on how this may affect toxicity. In addition, no information is provided on the toxicity of the hydrolysis products and consequently no explanation has been provided on what compound may cause the toxicity.

ECHA concludes that you did not address important aspects such as the toxicokinetics of the parent substance and their metabolic fate and the resulting possible difference in the metabolite profile. Therefore, it is not possible to verify the substances which are likely to govern the toxicity profiles of source and target substances. In the absence of such information there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

In your comments to the draft decision you theoretically considered the toxicokinetic properties of source and target substances, but did not provide supporting information on the metabolic fate of the substances. You provide a list of theoretically possible metabolites, which is based on potential hydrolysis, but not on other potential metabolism pathways, which you also mention. Furthermore you provided data on the abiotic hydrolysis of the substances.

ECHA notes that it is not possible to conclude from these data on the rate and extent of the metabolism of the substances once they are taken up from the gastrointestinal tract and reach the systemic circulation. It is therefore not possible to determine the amounts of parent substance and metabolites to which systemic exposure occurs.

In your comments you claim that the lack of enzymatic hydrolysis information does not matter due to the closely related structure and the comparable toxicity profile.

ECHA does not agree in general with this unsubstantiated claim.
Further, as mentioned above in section (iii) above, you have not provided sufficient data to support your read-across for pre-natal developmental and reproductive toxicity. ECHA notes that in addition to the structural differences the current data set does not exclude that differences in metabolism between the source and target substances may have an impact on pre-natal developmental and reproductive toxicity.

For repeated dose toxicity, however, ECHA considers that the lack of such metabolic data is partially mitigated by new toxicological information on the possible metabolites (see section iii). In addition, the prediction for repeated dose toxicity is supported by the available 28-day study with Tinuvin 292, which indeed shows a similar toxicity profile to Tinuvin 770 for this property (see section iii). Furthermore, you have identified a plausible mechanism of action for repeated dose toxicity.

(vi) Bias in the selection of source substances and source study

Annex I section 1.1.4 requires "...*that the study or studies giving rise to the highest concern shall be used to establish the DNELs.;"* In the context of a read-across approach this has two aspects: the selection of the source substance and the selection of the source study.

ECHA observes that you propose to read-across results from a sub-chronic study and a one-generation reproduction toxicity study conducted with the analogue substance. In these studies the corresponding dose descriptors are identified as a LOAEL of 29 mg/kg/day and a NOAEL of 300 mg/kg/day for the sub-chronic and one-generation study respectively. Despite this ECHA notes that your DNEL derivation uses a NOAEL of 300 mg/kg/day from the sub-acute study on the registered substance as the starting point for DNEL derivation. ECHA concludes based on the available information that the study which gives rise to the highest concern is currently not used as a starting point for the DNEL derivation.

Furthermore, ECHA notes that your read-across approach assumes that both the registered substance and the analogue substance undergo complete hydrolysis, resulting in the formation of sebatic acid, pentamethylpiperidinol and methanol from the registered substance, and sebatic acid and tetramethylpiperidinol form the analogue substance. ECHA wants to highlight that there are experimental results available on some of the identified hydrolysis products. ECHA considers that this information should be considered in the hazard identification of the registered substance (*e.g.* for 2,2,6,6-tetramethylpiperidinol, CAS No. 2403-88-5, decreased locomotor activity and mydriasis has been observed in both acute and sub-acute toxicity studies).

ECHA concludes that it is not possible to verify that you have selected the source substances which are most appropriate and furthermore that the source studies selected are giving rise to the highest concern as required in Annex I, Section 1.1.4.

ECHA notes that from your comments to the draft decision it is not clear which NOAEL value will be used as a starting point for DNEL derivation when you establish the quantitative prediction for the repeated dose toxicity. ECHA further stresses that, in the upcoming dossier update, the study with highest concern should be used for DNEL derivation.

D. Conclusion on the read-across approach

Based on the information presented in your comments on the draft decision the read-across approach can be considered to comply with the general rules of adaptation as set out in Annex XI, 1.5 for the standard information requirement sub-chronic toxicity (90-days; Annex IX, Section 8.6.2.) However, ECHA notes that the information presented in the comments need to be included in the technical dossier in the formats requested by the REACH Regulation, if appropriate with confidentiality flags.

While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage. Therefore the request for information from a sub-chronic toxicity (90-days) study derived with the registered substance remains in the decision.

ECHA considers that, for the reasons presented above, you have failed to explain as to how and why, in qualitative and quantitative terms, the toxicological properties of the registered substance can be accurately predicted by using the available information from the proposed source substances for the properties pre-natal developmental toxicity in the rat and the rabbit (Annex IX and X, Section 8.7.2) and extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.) Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for pre-natal developmental toxicity (Annex IX and X, Section 8.7.2) and toxicity to reproduction (Annex X, Section 8.7.3.) in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects these adaptations in the technical dossier that are based on Annex XI, 1.5.

Note to the Registrant

ECHA notes that evidence of similar developmental and reproductive toxicity profiles of the target and source substances is currently missing. ECHA considers that to strengthen the read-across approach, such additional evidence, e.g. Reproduction/Developmental Toxicity Screening Test (OECD 421) or Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422) could be considered in order to address the shortcomings as described above in sections (iii) and (v) and to meet the criteria on Annex XI, Section. 1.5. Although a study such as an OECD 422/OECD 421 study does not provide equal information compared to the more comprehensive PNDT/EOGRTS studies it may allow a determination whether a similar pattern of toxicity is likely also for the properties PNDT/EOGRTS.

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.

In the technical dossier you have provided a study record for a Repeated Dose 28-Day Oral Toxicity in Rodents (according to OECD TG 407; point i. in section 0.2 above) conducted with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower. Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study similar to a Repeated Dose 90-Day Oral Toxicity in Rodents (OECD TG 408; point ii. in section B above) conducted on the source substance (Tinuvin 770). However, as explained above (see sections C and D above), your adaptation of the information requirement was originally not accepted.

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.

Based on the information presented in your comments on the draft decision the read-across approach can be considered to comply with the general rules of adaptation as set out in Annex XI, 1.5 for the standard information requirement sub-chronic toxicity (90-days). Therefore, the information obtained with the source substance (Tinuvin 770,) may be used to meet the request for a sub-chronic (90-day) oral toxicity study and fulfil the information requirement of Annex IX, Section 8.6.2.

ECHA notes that the information presented in the comments to the draft decision need to be included in the technical dossier in the formats requested by the REACH Regulation. While

for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage. Therefore the request for information from a sub-chronic toxicity (90-days) study derived with the registered substance remains in the decision.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure (estimated to be < 0.0001 Pa at 20°C) and uses with industrial and professional spray application are reported in the chemical safety report. However, the estimated exposure concentrations are low (< [redacted]). Hence, the test shall be performed by the oral route using the test method OECD TG 408/EU B.26.

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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

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

A "pre-natal developmental toxicity study" 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.

The technical dossier does not contain information on a pre-natal developmental toxicity study with the registered substance.

You have sought to adapt this information requirement according to Annex IX, Section 8.7., column 2 and/or Annex XI, Section 1.5. You provided the following justification for the adaptation: *"A developmental toxicity study is considered unjustified based on the available information. In repeat-dose toxicity studies up to 90 days in the rat, no indication of the substance causing effects on the reproductive organs were seen.*

Furthermore, a 1-Generation performed with a structural analogue study did not affect the development of the offspring that can be interpreted as organogenesis disturbance at any stage. This is in line with the assessment of the toxicokinetic behavior suggesting the substance is not extensively absorbed and undergoes a rapid metabolism and elimination, without any potential for accumulation in the exposed organism. It is concluded that exposure to the substance is not hazardous for reproduction in any species including humans. This argumentation is in accordance with column 2 of REACH Annex IX for criteria to avoid animal testing."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.7., column 2 or general rule for adaptation of Annex XI; Section 1.5. because:

a) As explained above (see sections C and D above), your adaptation of the information requirements for a sub-chronic toxicity study (Annex IX, Section 8.6.2) and an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3) cannot be accepted. Consequently, studies conducted on the source substance (Tinuvin 770), cannot be used to predict the properties of the registered substance. In addition, neither of these studies alone or combined covers the key parameters foreseen to be investigated in a Prenatal developmental toxicity study (OECD TG 414) and, thus, does not provide equivalent information.

b) According to of Annex IX, Section 8.7., column 2 studies do not need to be conducted if the substance if: '*the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented*', or '*the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented'*, or '*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*'. ECHA notes based on the information provided in the dossier that the registered substance is not '*known to be a genotoxic carcinogen'* or *'known to be a germ cell mutagen'.* With regard to '*low toxicological activity'*, ECHA notes that evidence of toxicity was observed in the Repeated Dose 28-Day Oral Toxicity in Rodents (according to OECD TG 407; [redacted] 2010) conducted with the registered substance. ECHA concludes than none of the criteria in Column 2 of Annex IX, Section 8.7. are met.

Therefore, your adaptation of the information requirement cannot be accepted.

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 6.0, July 2017) R.7a, chapter 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.

ECHA notes that in your comments to the draft decision you agreed to perform the pre-natal developmental toxicity test on a first species with the registered substance, and based on the results on that study the decision on the pre-natal developmental toxicity study on the second species will be taken. However, in the comments to the draft decision of the source substance it is stated that a pre-natal developmental toxicity study on a first species will be conducted with the source substance Tinuvin 770 and the data will be read-across to the registered substance Tinuvin 292. ECHA considers that as the comments on the source substance were received at a later stage they are considered to represent the latest opinion of the Registrant.

As explained in "Grouping of substances and read across approach", your adaptation of the information requirement, which is based on Annex XI, Section 1.5, can currently not be accepted.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rats or rabbits) by the oral route.

3. 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 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 does not contain information on a pre-natal developmental toxicity study with the registered substance.

You have sought to adapt this information requirement according to Annex X, Section 8.7., column 2 and/or Annex XI, Section 1.5. You provided the following justification for the adaptation: "*A developmental toxicity study is considered unjustified based on the available information. In repeat-dose toxicity studies up to 90 days in the rat, no indication of the substance causing effects on the reproductive organs were seen. Furthermore, a 1-Generation performed with a structural analogue study did not affect the development of the offspring that can be interpreted as organogenesis disturbance at any stage.*

This is in line with the assessment of the toxicokinetic behavior suggesting the substance is not extensively absorbed and undergoes a rapid metabolism and elimination, without any potential for accumulation in the exposed organism. It is concluded that exposure to the substance is not hazardous for reproduction in any species including humans. This argumentation is in accordance with column 2 of REACH Annex IX for criteria to avoid animal testing."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7., column 2 or general rule for adaptation of Annex XI; Section 1.5. because:

a) As explained above (see sections C and D above), your adaptation of the information requirements for a sub-chronic toxicity study (Annex IX, Section 8.6.2) and an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3) cannot be accepted. Consequently, studies conducted on the source substance (Tinuvin 770), cannot be used to predict the properties of the registered substance. In addition, neither of these studies alone or combined covers the key parameters foreseen to be investigated in a Prenatal developmental toxicity study (OECD TG 414).

b) According to Annex X, Section 8.7., column 2, studies do not need to be conducted if the substance if: '*the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented*', or '*the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented*', or '*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*'. ECHA notes based on the information provided in the dossier that the registered substance is not '*known to be a genotoxic carcinogen*' or '*known to be a germ cell mutagen*'. With regard to '*low toxicological activity*', ECHA notes that evidence of toxicity was observed in the Repeated Dose 28-Day Oral Toxicity in Rodents (according to OECD TG 407; [redacted], 2010) conducted with the registered substance. ECHA concludes than none of the criteria in Column 2 of Annex X, Section 8.7. are met.

Therefore, your adaptation of the information requirement cannot be accepted.

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 consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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) R.7a, chapter 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.

ECHA notes that in your comments to the draft decision you agreed to perform the pre-natal developmental toxicity test on first species with the registered substance, and based on the results on that study the decision on the pre-natal developmental toxicity study on second species will be taken. However, in the comments to the draft decision of the source substance it is stated that pre-natal developmental toxicity study on first species will be conducted with the source substance Tinuvin 770 and the data will be read-across to Tinuvin 292. ECHA considers that as the comments on the source substance were received at a later stage they are considered to represent the latest opinion of the Registrant.

As explained in "Grouping of substances and read across approach", your adaptation of the information requirement, which is based on Annex XI, Section 1.5, can currently not be accepted. Further, a pre-natal developmental toxicity test on a second species is a standard information requirement under Annex X that, at this stage, cannot be waived based on a future pre-natal developmental toxicity test on a first species.

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 or rats) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

4. 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 (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 sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. However, as explained above (see sections C and D above), your adaptation of the information requirement cannot be accepted. Therefore, 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

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

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 6.0, July 2017).

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 the registered substance itself derived from available Repeated Dose 28-Day Oral Toxicity in Rodents (according to OECD TG 407; see point i. in section B above) show evidence of mydriasis (dilation of the pupil) at dose levels of 750 mg/kg bw/d (males) and 1000 mg/kg bw/d (females); the LOAEL of the study was based on these findings. More specifically, "*Sensorimotor tests/reflexes: On study day 23/24, retarded adaptation of the pupil to light (pupillary reflex) was seen in 1 male and 3 females of test group 3 (750/1000 mg/kg bw/d). In addition, no adaptation of the pupil to light (pupils permanently dilated) was observed for 7 females of test group 3 (1000 mg/kg bw/d).*" Furthermore"*On study day 23/24 animals of the test group 3 (750/1000 mg/kg bw/d) showed reduced rearing by -37% (males) and significantly reduced rearing -45.1% (females).".* In addition, ECHA notes that the substance 2,2,6,6-tetramethylpiperidin-4-ol (CAS No 2403-88-5) which is a structural analogue to one of the hydrolysis products of the registered substance (1,2,2,6,6,-pentamethylpiperidin-4-ol) has acute and sub-acute toxicity studies available (described in the registration dossier of the analogue) which show decreased locomotor activity and mydriasis. The muscles that control the size of the iris are controlled by the sympathetic or para-sympathetic nervous system. In the absence of histophathological findings in skeletal muscle ECHA considers this to be a neurotoxic effect. The observed behavoral changes also supports this notion. ECHA considers that the observation of mydrasis in the sub-acute study with the registered substance and the structural analogue to one of the hydrolysis products of the registered substance constitute a particular concern for (developmental) neurotoxicity which has to be addressed.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* studies on the registered substance itself and a structural analogue to one of its hydrolysis products.
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 6.0, July 2017) R.7a, chapter 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.

ECHA notes that in your comments to the draft decision you consider the one-generation reproductive toxicity study sufficient to fulfil the information requirement of reproductive toxicity (Annex X, 8.7.3). However, in the comments to the draft decision of the source substance it is stated that one-generation reproductive toxicity study "*may not be sufficient*" and you agree to conduct an extended one-generation reproductive toxicity study (OECD 443) with the source substance Tinuvin 770. ECHA considers that as the comments on the source substance were received at a later stage they are considered to represent the latest opinion of the Registrant.

As explained in "Grouping of substances and read across approach", a one-generation reproductive toxicity study is not sufficient to fulfil the information requirement of reproductive toxicity and your adaptation of the information requirement based on a read-across with the source substance Tinuvin 770, which is based on Annex XI, Section 1.5, can currently not be accepted.

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, the extension of Cohort 1B and the inclusion of Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 1) and/or any other relevant information may trigger 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 **15 January 2019**. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by ***15 April 2019*** (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 **15 April 2019**, 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 and the results will need to be submitted by the deadline given in this decision ***15 July 2021***.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 6.0, July 2017)*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it 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.

5. Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance including each relevant constituent present in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable;

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

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable in an OECD TG 301E (Ready biodegradability: Modified OECD Screening Test) study (38% biodegradation after 28 days). Consequently, the specific rule for adaption presented in column 2 of Annex IX, Section 9.2.3. of the REACH Regulation does not apply.

ECHA notes that in the technical dossier you have provided information on degradation products generated from hydrolysis only (abiotic degradation). However, ECHA notes that you must identify the transformation/degradation products generated not only from hydrolysis but also from biotic degradation. ECHA notes that the biodegradation section in the technical dossier does not contain any information in relation to the identification of biotic degradation products, nor an adaptation in accordance with column 2 of Annex IX, Sections 9.2.3. or 9.2 or with the general rules of Annex XI for this standard information requirement.
ECHA notes that information on degradation products is required for the PBT/vPvB assessment as Annex XIII of the REACH Regulation explicitly requires that PBT/vPvB properties of relevant degradation products need to be taken into account. ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11.4.1. further specifies that "*constituents, impurities and additives should normally be considered relevant for the PBT/vPvB assessment when they are present in concentration of ≥ 0.1% (w/w). This limit of 0.1% (w/w) is set based on a well-established*

practice rooted in a principle recognised in European Union legislation. [...] Similar arguments apply to relevant transformation/degradation products. The PBT/vPvB assessment should normally be carried out for each relevant transformation or degradation product".

Therefore, ECHA considers that the information on degradation products is needed for the PBT/vPvB assessment (Annex XIII of the REACH Regulation), as well as for the compilation of safety data sheets (Annex II of the REACH Regulation).

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

Regarding appropriate and suitable test method, the methods will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You will need to provide a scientifically valid justification for the chosen method.

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

Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section, including each constituent and relevant impurity present in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable.

Notes for your consideration

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

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when information request above is available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

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

The compliance check was initiated on 4 November 2015.

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

On 15 January 2016 you provided comments on the draft decision.

On 20 December 2016 you provided comments on the source substance Tinuvin 770.

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 proposal(s) for amendment.

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

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

ECHA referred the draft decision to the Member State Committee.

You provided comments only on the draft decision. Your comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-57 meeting and ECHA took the decision according to Article 51(6) 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 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.

3. In relation to the information required by the present decision, the sample of 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 composition 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 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.