EUROPEAN CHEMICALS AGENCY

Helsinki, 26 September 2017

Addressee: [redacted]

Decision number: CCH-D-2114373832-44-01/F
Substance name: Diisopropyl-1,1'-biphenyl and tris(1-methylethyl)-1,1'-biphenyl (mixture)
List number: 915-589-8
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/07/2017
Registered tonnage band: [redacted]

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. **Name or other identifier of the substance (Annex VI, Section 2.1.):**
   - **Chemical name;**
   - **Manufacturing process;**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2; test method: EU B.31/OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**
3. **Extended one-generation reproductive toxicity study (Annex IX, 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; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity)**
4. **Identification of degradation products (Annex IX, Section 9.2.3)**
5. **Exposure assessment and risk characterisation (Annex I, Sections 5 and 6) for human health:**
   - **revising exposure estimates using a model within its domain of applicability or provide adequate measured representative exposure data;**
   - **revising exposure estimates for dermal route without the use of LEV as exposure modifier;**

   and revise risk characterisation accordingly;

6. **Exposure assessment and risk characterisation (Annex I, Sections 5 and 6) for environment:**
   - **use default release factors and other recommendations of ECHA Guidance R.16 and revise the risk characterisation accordingly for exposure scenarios 1 and 4 or provide an adequate and detailed justification for not using the recommendations of ECHA Guidance R.16 for estimation of environmental exposure.**

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 **3 April 2020**. **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.

Environmental fate and hazard information is outside the scope of this compliance check.

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/web/guest/regulations/appeals.

Authorised[2] by Kevin Pollard, Head of Unit, Evaluation E1

[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

In order to ensure that potential hazardous properties of the substance are not underestimated, the information that is necessary to resolve the substance identification deficiencies below, must be available to you before identifying the test sample to be used for the testing requested in the present decision.

1. Name or other identifier of the substance (Annex VI, Section 2.1.);

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

"Name or other identifier of the substance" is an information requirement as laid down in Annex VI, Section 2.1. of the REACH Regulation. The name and other identifiers are used to identify the substance in an unambiguous manner and are therefore fundamental for substance identification. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to the Guidance for identification and naming of substances under REACH and CLP (version 2.1, May 2017), thereinafter referred to as "the Guidance":

Multi-constituent substances are those where more than one well-defined constituent is present in a concentration ≥10% (w/w) and <80% (w/w).

Variability of composition for well-defined substances is specified by upper and lower limit of the concentration range(s) of the main constituent(s).

As opposite, UVCB substances (substances of Unknown or Variable composition, Complex reaction products or Biological materials) cannot be sufficiently identified by their chemical composition, because:

- The number of constituents is relatively large and/or
- The composition is, to a significant part, unknown and/or
- The variability of composition is relatively large or poorly predictable.

The registered substance has been identified as a well-defined multi-constituent substance and has been given the name "Reaction mass of diisopropyl-1,1'-biphenyl and tris(1-methylethyl)-1,1'-biphenyl".

ECHA notes the following:

- The two names
  - diisopropyl-1,1'-biphenyl
  - tris(1-methylethyl)-1,1'-biphenyl

  are generic and describe biphenyl structures bearing respectively two and three isopropyl substituents. Because the position of these substituents on the biphenyl structure is not specified, such names refer to all possible isomers of diisopropyl-1,1'-biphenyl and tris(1-methylethyl)-1,1'-biphenyl differing with each other on the position of the substituents.

  Considering the large number of possible isomers, a substance described by this name would not be regarded as a multi-constituent substance but rather as a substance of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB).

- You provided the name: "Mixture of Diisopropyl-1,1'-biphenyl (isomers) and Tris(1-methylethyl)-1,1'-biphenyl" in the public name field of the IUCLID dossier. Such name indicates that a series of isomers are included in the substance composition.

- Two reference substances having generic EC and CAS identifiers are reported as main constituents in the composition information of the IUCLID dossier:

  [redacted]

  As explained above such names refer to groups of isomers and therefore are regarded as groups of constituents. Furthermore ECHA notes that the IUPAC name and structural information specified for the group of constituents [redacted] correspond to the specific isomer "[redacted]". This information is in contradiction with the generic EC and CAS identifiers reported. No further information is given on the presence of the specific isomers present in the composition, therefore it is unclear whether the registered substance consists of all possible isomers of the two groups of constituents or a subset of these isomers.

- The chromatographic analysis included in the registration dossier shows several peaks. This indicates that a multitude of constituents are present in the composition of the registered substance. The analytical report, however, does not include information on the isomeric composition of the registered substance.

- The manufacturing process description provided is limited to the statement "[redacted]". No additional information is given on the identity of the reactants, relevant process conditions, specificity of the reaction, isolation and purification steps applied for manufacturing the substance. No conclusion can be made on the isomery of the substance.

On the basis of the information included in the registration dossier ECHA is not in the position to conclude whether the registered substance consists of all possible isomers of "[redacted]" or whether the substance consists of a subset of these isomers.

Consequently, further information is required to appropriately identify and naming the registered substance, in line with Annex VI, Section 2.1 of the REACH Regulation. In that respect ECHA can identify the following two possible situations:

(i) The substance subject to this registration should be considered as a UVCB substance.

> As indicated in chapter 4.3 of the Guidance, the naming of UVCB substances, shall consist of two parts: (a) the chemical name and (b) a more detailed description of the manufacturing process. As explained above the information given on the manufacturing process of the registered substance is limited and needs to be further explained. You are therefore required to provide a detailed description of the manufacturing process, including the chemical identity of the starting materials, ratio of reactants, specificity of the reaction and information on the most relevant steps and parameters of the manufacturing process.

(ii) The registered substance should be regarded as a well-defined substance.

> In case the isomers can be identified and quantified by appropriate analytical methods, *i.e.* the composition of the substance is known to include a limited number of the possible isomers of [redacted] as main constituents, the substance would be identified as a well-defined multi-constituent substance. In this case, the chemical name of the substance shall reflect the presence of each specific isomer present in the substance at concentration levels > 10% in accordance with the Guidance. In addition, the ratio of the isomers shall be reported in the composition, and a description of the analytical method used for deriving the identity and ratio of the isomers shall be included in section 1.4 of the IUCLID dossier.

If the current EC numerical identifier does not correctly identify the registered substance, it will need to be revised. However, for technical reasons, you are requested not to remove or revise the EC entry at the stage of submitting the updated dossier. As this registration is linked to this EC entry in REACH-IT, the IT system will not accept the updated dossier as an update when the EC entry has changed. You shall instead include the following in the "Remarks field" of the reference substance: "*This EC entry is not appropriate to identify the registered substance. This identifier cannot be modified in the present registration at this stage for technical reasons.*" You shall also specify, in the same "Remarks" field, any available and appropriate EC number for the substance.

You should note that ECHA has established a process, subject to certain conditions, enabling registrants to adapt the EC identifier of an existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

However, pending the resolution of all the incompliances related to substance identity highlighted in the present decision, the adaptation of the identifier can only be effective once ECHA is at least in a position to establish unambiguously the identity of the substance intended to be covered by you with this registration. Should the information submitted by you as a result of the present decision enable ECHA to identify the substance unambiguously, the process of adapting the identifier will be considered relevant. In that case, ECHA will inform you in due time as to when the identifier adaptation process shall be initiated.
In any case, you should note that the application of the process of adapting the identifier does not affect your obligation to fulfil the requirements specified in this decision.

As for the reporting of the information in IUCLID, the chemical name and manufacturing process description should be specified in the "IUPAC name" and "Description" field in IUCLID section 1.1, respectively.

You shall ensure that representative identifiers are used throughout the dossier, and are consistent with the information on the composition in section 1.2 and the analytical data in section 1.4 of the IUCLID dossier.

Further information on how to report the chemical name, the molecular and structural formulae, other identifiers and the description of the manufacturing process is available in "How to prepare registration and PPORD dossiers " (version: 4.0, May 2017), available on the ECHA website.

PROPERTIES OF THE SUBSTANCE

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt the information requirement for a pre-natal developmental toxicity study (Annex IX, 8.7.2.) by applying a read-across approach in accordance with the principles set out in to Annex XI, Section 1.5. of the REACH Regulation. The justification you provided to support your read-across approach is: *"For the assessment of intrauterine development following exposure to [redacted], no study has been located. Instead, [redacted], a structure-related substance, serves as surrogate (LPT 1993).*

This is justified, since in general [redacted] share similar physico-chemical and structural properties, while showing high acute tolerance and producing mild to moderate repeated-dose toxicity in rats with the liver as primary target organ in both cases, moreover, neither exhibiting a mutagenic potential. Therefore, it is concluded that [redacted] results for this endpoint may be extrapolated to the target compound, [redacted]."

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*".

According to Annex XI, Section 1.5., there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). Furthermore, Annex XI, Section 1.5 lists several additional requirements, including that adequate and reliable documentation of the applied method is to be provided.

ECHA observes that you claim that "[redacted] *results for this endpoint may be extrapolated to the target compound,* [redacted]" but you have not substantiated that claim with data. More specifically, your dossier contains no documentation establishing a basis whereby relevant human health properties of the registered substance may be predicted from data for the analogue substance [redacted]. In the absence of any documentation and factual evidence supporting the proposed read-across approach, ECHA considers that you have failed to provide an adequate and reliable documentation of the applied method as required by Annex XI, Section 1.5 of the REACH Regulation. Therefore, ECHA is not in a position to evaluate the proposed read-across approach which could allow establishing that relevant properties of the registered substance can be predicted from those of the analogue substance. The proposed read-across has therefore to be rejected.

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

According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration ECHA considers testing should be performed with rats or rabbits as a first species.

According to the test method EU B.31/OECD TG 414, the test substance is usually administered orally. On the basis of this default consideration, ECHA considers testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rats or rabbits) by the oral route.

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

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 IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

ECHA considers that adverse effects on reproductive organs or tissues and/or other concerns in relation with reproductive toxicity are observed. More specifically, the following effects are reported in the 28-day toxicity study according to OECD TG 407 with the registered substance ([redacted], 2014) which was extended with respect to animal number (10 instead 5 animals per sex and dose):

- Effects in reproductive organs
  - Follicular degeneration in ovaries, oestrous cycle disturbance at the highest dose level
  - Reduced absolute and relative weights of ovaries at high dose level
  - Reduced absolute and relative weight of uterus at mid and high dose level
  - Atrophy in male reproductive organs (testes, prostate, seminal vehicle and coagulating gland) at the highest dose level
  - Reduced absolute weight of epididymides at the highest dose level
  - Reduced absolute and relative weights of prostate and seminal vesicle at the mid and high dose level
- Effects in thyroid gland and thyroid hormones
  - Significant increase in thyroid weights (both absolute and relative to body weight)
  - Histopathological changes in both genders at all dose levels.
  - Shift in thyroid-hormone balance in blood (increase in TSH, decreasing trend in T3 and T4).

Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

b) Information provided

You have sought to adapt this information requirement by providing the following justification:

> *"Deviating from endpoints of column 2 in ANNEX IX and X, and with reference to ANNEX XI, section 1.1 and 1.2, the registrant waives this study (and likewise the alternative extended one generation study OECD 443) for the following reasons:*
>
> *The extended 28-day study in rats demonstrates that the liver is the primary target organ, associated with secondary impact on the hypothalamo-pituitary thyroid axis, resulting in disturbance of the thyroid hormone balance. These adverse effects, already noted at the lowest dose of 35 mg/kg/d, clearly dominates over any impairment of reproductive performance only detectable at the highest dose of 600 mg/kg bw/d (In the 28 d-study included were organ-weight measurements, histopathology of genital organs as well as staging of spermatogenesis and thyroid hormone status) (see also repeated dose toxicity).*
>
> *The registrant concludes that at the present stage, in compliance with ANNEX XI, Section 1.1 and 1.2, a fertility/generation study is not justified and not urgent, because significant and meaningful data is not expected to result from further long-term testing for the following reasons:*
> *1. The estimated long-term DNELs of significantly below 1 mg/m3 and below 1 mg/kg bw/d (dermal) related to hepatotoxicity is considered to be sufficiently conservative to protect exposed humans from any possible adverse effects on reproductive performance. The provisional classification for STOT (Cat. RE 2) also covers an unlikely or low potential for reproductive impairment.*
> *2. There is empirical evidence to suggest the toxicological significance of the findings in the rat is poor for human physiology (in compliance with ANNEX XI, Sect. 1.2)."*

c) ECHA's evaluation and conclusion of the provided information

You state that the primary effects are observed in the liver at the lowest dose level which dominates the effects observed in the "*reproductive performance*" at the highest dose level of 600 mg/kg bw/day only. However, ECHA notes that in the 28-day toxicity study, multiple effects on reproductive organs have been observed, at both the mid and high dose levels. Such effects include organ weight changes of prostate, seminal vesicle, and uterus at both the mid and high dose levels, and epididymides and ovaries at high dose level. Furthermore, follicular degeneration in ovaries with oestrous cycle disturbances and atrophy of testes, prostate, seminal vehicle and coagulating gland were observed at the high dose level. Thyroid-related effects were observed at all dose levels which you claim to be as secondary impact to liver effect. You have not provided scientific evidence that effects on thyroid and reproductive organs are indeed secondary to the liver effect. Hence, ECHA considers that those findings are indicative of a reproductive hazard.

In addition, in the 28-day study, reproductive and endocrine organs have been examined after a short exposure duration in adult male and non-pregnant female animals. Thus, this study does neither provide information on actual functional fertility such as mating behaviour, conception, pregnancy, parturition, litter sizes and lactation nor on other extensive peri- and post-natal investigations of the F1 generation up to adulthood which are needed to conclude on reproductive toxicity. These include also investigations to detect certain endocrine modes of action, sexual maturation, and concern-based investigations on developmental neurotoxicity.

You further comment that "*a fertility/generation study is not justified and not urgent, because significant and meaningful data is not expected to result from further long-term testing" because "The estimated long-term DNELs of significantly below 1 mg/m3 and below 1 mg/kg bw/d (dermal) related to hepatotoxicity is considered to be sufficiently conservative to protect exposed humans from any possible adverse effects on reproductive performance. The provisional classification for STOT (Cat. RE 2) also covers an unlikely or low potential for reproductive impairment".*

ECHA notes that the point of departure used for DNEL derivation is assigned from the 28-day toxicity study. However, as presented in section 2(d) below, the information derived from this study does not cover the information requirement of an extended one-generation reproductive toxicity study. Hence, the DNEL derived from this study is not considered appropriate to omit an extended one-generation reproductive toxicity study. Regarding to your second statement, ECHA notes that your substance is classified as STOT (category RE 2) and the identified target organs are liver and thyroid. However, STOT Classification for specific organ toxicity (STOT) is a different hazard class compared to the classification for reproductive toxicity, e.g. sexual function and fertility, and it does not cover reproductive hazards. ECHA considers that there is enough evidence from the 28-day study to be concerned on the potential properties related to reproductive toxicity and it is justified to investigate the reproductive toxicity of the registered substance in an extended one-generation reproductive toxicity study to clarify if classification to reproductive toxicity is warranted. Hence, your assumption that "*STOT (Cat. RE 2) also covers an unlikely or low potential for reproductive impairment*" is not acceptable.

With respect to your argument that "*There is empirical evidence to suggest the toxicological significance of the findings in the rat is poor for human physiology (in compliance with ANNEX XI, Sect. 1.2).*" ECHA notes that your explanation is not endpoint specific and not substantiated with data. ECHA understand that you potentially refer to adverse effects observed in the 28-day study. However, you have self-classified the substance as STOT RE 2 which is based on the adverse effects (liver and thyroid) from the 28-day study in the rat ([redacted] 2014). Hence, your statement of "*the findings in the rat is poor for human physiology"* contradicts your self-classification of the substance as STOT RE 2 which is based on the adverse effects in the rat. Thus, your argument is not adequate to invalidate the information from the available rat study and/or the rat as a model to investigate the hazardous properties of your registered substance.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have argued that "*for toxicological reasons, we do not advocate the performance of this study, unless there is clear evidence of a toxicological trigger. At present, we believe toxicity-relevant questions have to be resolved by expert judgment, while standard requirements will fail to properly describe the toxicological properties of DIPS.*

However, as explained above in section 2(a) above, ECHA considers that the results from the 28-day repeated dose toxicity study with the registered substance indicate adverse effects on reproductive toxicity which trigger the need to perform an extended one-generation reproductive toxicity study.

In your comments you also state that "*based on current knowledge low and probably safe DNELs have been derived, while DIPS has provisionally been classified in a reasonable category. We refer to the use pattern provided on top of this letter clearly demonstrating that most uses are without exposure risk*".

ECHA considers that you are referring to the adaptation of the information requirements according to the general rules for adaptation according to Annex XI, Section 3.2.a. However, ECHA notes that the current DNELs are derived from the results of the 28-day repeated dose toxicity study and according to Annex XI, Section 3.2.a(ii) and the subsequent footnote, a DNEL derived from a lower tier study shall not be considered appropriate to omit the higher tier study. Further, Annex XI, Section 3.2.a(i) requires to demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses. However, based on the information provided in the CSR and the use description of the substance, there are scenarios with high potential for exposure (e.g. PROC 7, 8a, 8b, 10). Hence, you have not demonstrated the absence of or no significant exposure for the full life cycle of the substance. Therefore, ECHA considers that the general rules for adaptation according to Annex XI, Section 3.2.a. are not met.

d) Conclusion

ECHA notes that your adaptation does not meet the general rules for adaptation of Annex XI, Section 1.1.2, because the provided 28-day toxicity study does not cover the key parameters of the information requirement, extended one-generation reproductive toxicity study, like functional fertility such as mating behaviour, conception, pregnancy, parturition, litter sizes and lactation nor on other extensive peri- and post-natal investigations of the F1 generation up to adulthood which are needed to conclude on reproductive toxicity. These include also investigations to detect certain endocrine modes of action, sexual maturation, and triggered concern-based investigations on developmental neurotoxicity. Furthermore, the exposure duration and life stages covered is not comparable to the extended one-generation reproductive toxicity study. Therefore, this study cannot be considered to provide equivalent information to be generated by an extended one-generation reproductive toxicity study (B.56 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 443). Thus, the adaptation rule of Annex XI, Section 1.1.2 is not met.

ECHA notes that your adaptation does also not meet the general rules for adaptation of Annex XI, Section 1.2., because you only provided one source of information which, together with your justification for the adaptation, does not allow to assume/conclude that the substance has or does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex IX, Section 8.7.3. As explained above, the information provided meets the criteria to request more information on reproductive toxicity, an extended one-generation reproductive toxicity study. Information on essential elements of the reproduction have not been provided to support the "no reproductive toxicity hazard" claim (see above) and the available data already indicates concern. Hence, the general rules for adaptation laid down in Annex XI, Section 1.2., of the REACH Regulation are not met.

ECHA also notes that the general rules for adaptation according to Annex XI, Section 3.2.a., invoked by you in your comments, are not met.

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 to Annex IX, Section 8.7.3., is required. The following refers to the specifications of this required study.

e) *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 the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), the starting point for deciding on the length of the 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 if the extension of Cohort 1B is not included in the study design and 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* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). Ten weeks exposure duration is supported also by the lipophilicity of the substance (with log Kow of the registered substance is 6.67) 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 IX. 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 *in vivo* studies i.e. 28-day oral toxicity study provided [redacted], (2014) show evidence of adverse effects on the nervous system considering:

- Statistically significant decrease in mean locomotor activity in both genders at the mid and highest dose groups. Decrease in the total mean locomotor activity in males at the mid and high dose groups and attaining statistical significance at the highest dose group.

ECHA also notes that existing information in the same study show evidence on specific mechanisms/modes of action with an association to developmental neurotoxicity:

- The effects observed in the thyroid gland and thyroid hormone balance:
  - Significant increase in thyroid weights (both absolute and relative to body weight) and histopathological changes in both genders at all dose levels,
  - Shift in thyroid-hormone balance in blood (increase in TSH, decreasing trend in T3 and T4).

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* study on the registered substance itself.

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 consideration, 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) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

f) Outcome

Based on the available information, 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).

Notes for your consideration

In the updated registration dossier you have removed uses by professionals and consumers which was one of the basis for triggering the extension of Cohort 1B in the initial draft decision. Hence, the conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified.
However, you may expand the study by including extension of Cohort 1B, and/or Cohort 3 if relevant information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). 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 expansion 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.

4. Identification of degradation products (Annex IX, Section 9.2.3.)

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.

The biodegradation section in the technical dossier does not contain any information in relation to the identification of degradation products, nor an adaptation in accordance with column 2 of Annex IX, Sections 9.2 or 9.2.3. or with the general rules of Annex XI for this standard 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.

The information in the technical dossier includes the key study (screening test on ready biodegradation, test guideline OECD 310) with a structural similar substance [redacted] that does not reach the pass level of 60% within 28 days after the test started (dossier: 58% degradation at day 28 calculated with 2 of 3 replicates; 65% degradation at day 35 calculated with 3 replicates). Nevertheless in the key study you provide the conclusion that the substance fulfils the criteria of being rated "readily biodegradable, but failing 10-day window". You conclude this from the provided time decomposition curve. In contrast in the endpoint summary you conclude that the substance is "inherently biodegradable". This conclusion is also used in the rationale for the evidence of non-P/non-vP properties (CSR section 8.1.1.1.1): "*The technical product is assessed to be less accessible to biodegradation but still will be inherently biodegradable.*" The result of 58 % degradation in 28 days refers to a minor component [redacted] which contributes on average only [redacted]% to the registered substance. The minor component did not reach the pass level.

There is no ready biodegradation data for the major component [redacted] but a BIOWIN estimate suggests it to be "not readily biodegradable". The substance used for the read-across has water solubility higher by a factor of 10 from the registered substance ([redacted] mg/l and 0.033 mg/l) and a lower partition coefficient octanol/water (log Kow = [redacted] and 6.67). ECHA considers this leads to better bioavailability and better degradation results of the read-across substance compared to major component of the registered substance. This leads to the conclusion that the registered substance will not reach the trigger value for being rated as "readily biodegradable".

Furthermore, ECHA notes that you have not provided any justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to provide information on the degradation products. ECHA considers that this information is needed in relation to the PBT/vPvB assessment.

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.

In your comments on the Proposal for Amendment (PfA) submitted by a Member State Competent Authority, that led to the inclusion of the present request in the decision, you confirm that you wish to perform an enhanced OECD TG 310 "*to examine the biodegradation kinetics of its individual constituent, (...) focusing on the decrease of the original constituent pattern and the identification of the degradation products*". ECHA notes that an enhanced OECD 310 test test may provide information on degradation products and relevant information for P assessment. However, prior to conducting the enhanced OECD 310 TG, ECHA advises you to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R11 (version 3.0, June 2017) and specifically the section "Integrated assessment and testing of Persistence-Explanatory Notes to Figure R.11—3" in which the conditions for an enhanced test valid for the PBT assessment are described.

In your comments you also state that "*In case a significant amount of the constituents show no or only minor degradation, evidence for a P or vP conclusion may be given*". However, ECHA would like to remind you that "*If one or more of the constituents are proven to fulfil either the vPvB or PBT criteria, the entire (registered) substance must be concluded as "The substance fulfils the PBT and/or vPvB criteria"and the (group(s) of) constituent(s) causing this conclusion must be specified in the dossier*", (ECHA Guidance on information requirements and chemical safety assessment R.11 (version 3.0, June 2017) R.11.4.2.2.2).

Moreover, according to Annex XIII of the REACH Regulation, the identification of PBT/vPvB substances shall take account of the PBT/vPvB-properties of relevant constituents of the substance. Section R.11.4.1 (page 36) of REACH Guidance document R.11 on PBT/vPvB assessment (version 3.0, June 2017) further indicates 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 recognised in European Union legislation to use this limit as a generic limit. Individual concentrations < 0.1% (w/w) normally need not be considered".

Therefore the degradation products shall be identified for each constituent, impurity and additive present in the registered substance in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable.

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.

5. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for human health

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

According to Article 14(4) of the REACH Regulation, if the substance fulfils the criteria for any of the hazard classes of Annex I to Regulation (EC) No 1272/2008 listed in Article 14(4) of the REACH Regulation or is assessed to be a PBT or vPvB, the chemical safety assessment shall include an exposure assessment and risk characterisation. ECHA notes that the registered substance is classified for health and environment hazards. Therefore an exposure assessment and risk characterisation shall be included in the chemical safety assessment.

The exposure assessment shall be conducted in accordance with Section 5 of Annex I. Annex I, section 5.2.4 of the REACH Regulation, requires the Registrant to perform an estimation of the exposure levels for all human populations (workers, consumer and humans liable to exposure via the environment) for which exposure to the substance is known or reasonably foreseeable. Each relevant route of exposure (inhalation, oral, dermal and combined through all relevant routes and sources of exposure) shall be addressed. In addition, Annex I, section 5.2.5 of the REACH Regulation indicates that appropriate models can be used for the estimation of exposure levels.

ECHA notes that you have used ECETOC TRA version 3.0 and ART version 1.5 to estimate the exposure levels for your exposure scenarios. However, ECHA notes that several deficiencies have been identified in the exposure assessment when the ECETOC TRA tool was used since you have applied additional reduction factors to the estimations obtained with the model which are either different from what is built-in in the model or are not correct. More specifically:

- You have assumed a linear relationship between concentration and estimated exposure for inhalation and dermal route in several contributing scenarios for several exposure scenarios when ECETOC TRA tool was used. According to the guidance for the model you used (ECETOC TRA Technical Report No. 114) and if the concentration of the substance in a mixture is > 25%, the mixture should be treated like the pure substance, for concentrations 5-25% an exposure reduction of 40% should be applied, for concentrations 1-5% and exposure reduction of 80% and for concentrations <1% an exposure reduction of 90%. As a consequence, the estimated exposure values would be higher (e.g. the dermal exposure estimate for the contributing scenario for PROC 10 in exposure scenario 3 would be [redacted] mg/kg bw/day instead of [redacted] mg/kg bw/day) leading to RCRs above 1. Therefore, the risks arising from the use of the substance in a mixture might not be adequately controlled.
- You have assumed a linear relationship between duration of the task and dermal exposure estimation. According to the guidance for the model you used (ECETOC TRA Technical Report No. 114) for high and moderate volatility liquids and non-dusty solid substances, if the duration of the task is less than 4 hours can lead to exposure reductions (i.e. 40% for 1-4 hour tasks, 80% for 15 min - 1 hour tasks and 90% for <15 min tasks) but not in a linear relationship manner. However, it is stated that those exposure reductions do not apply for low or very low volatility liquids like the registered substance subject to this decision. As a consequence, the estimated exposure values for dermal route would be higher and leading to RCRs above 1. Therefore, the risks via dermal route arising from the use of the substance might not be adequately controlled.
- You have used the local exhaust ventilation (LEV) exposure modifier for estimating dermal exposure even though inappropriate considering the low volatility of the registered substance. ECHA underlines that the Guidance on information requirements and chemical safety assessment, R.14 version 3.0 August 2016 (Appendix A.14-1.1) advises against the use of the LEV modifier for dermal exposure estimation of low volatility substances. As a consequence, the estimated exposure values for dermal route would be higher and leading to RCRs above 1. Therefore, the risks via dermal route arising from the use of the substance might not be adequately controlled.

As explained above, some of the information provided on the exposure estimation for the registered substance in the chemical safety report does not meet the general provisions for preparing a chemical safety report as described in Annex I.

In the comments on the draft decision according to Article 50(1) of the REACH Regulation you seem to indicate that since the model used to estimate exposure (i.e. ECETOC TRA) is overestimating exposure and there are other models that allow a linear relationship between concentration and estimated exposure for inhalation and dermal route, you can modify the model parameters using the above-mentioned linear relationship to mitigate "*obvious overestimations*".

However, ECHA notes first that if a model is used to estimate exposure, it has to be used within its boundaries , i.e. without modifying the underlying basis of the model. Also, in this particular case, the model used (i.e. ECETOC TRA) is a Tier I tool and therefore it is expected to be conservative. Second, as mentioned in ECHA's Guidance R.14., Appendix A.14-1.4, "*if an initial assessment of exposure is not adequate, i.e. safe use is not reliably demonstrated, a refined assessment is necessary*". Further, several examples of models to be used in a refined assessment include Stoffenmanager, Advance REACH Tool (ART) and RISKOFDERM (the latter for exposure estimation via dermal route). ECHA notes that you also refer to those models in your argumentation. As an alternative, exposure measurements in real exposure situations can be carried out.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to revise the exposure assessment and risk characterisation:
- revising exposure estimates using a model within its domain of applicability and in accordance with the guidance for the model used or provide adequate measured representative exposure data;
- revising exposure estimates for dermal route without the use of LEV as exposure modifier; and revising risk characterisation accordingly.
Notes for your consideration

The revised DNELs requested with this decision shall be taken into account when assessing the related risks.

6. Exposure assessment and risk characterisation (Annex I, Sections 5 and 6) for environment

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report (CSR) which shall document the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

According to Article 14(4) of the REACH Regulation, if the substance fulfils the criteria for any of the hazard classes of Annex I to Regulation (EC) No 1272/2008 listed in Article 14(4) of the REACH Regulation or is assessed to be a PBT or vPvB, the chemical safety assessment shall include an exposure assessment and risk characterisation. ECHA notes that the registered substance is classified for health and environment hazards. Therefore an exposure assessment and risk characterisation shall be included in the chemical safety assessment.

The exposure assessment shall be carried out according to section 5 of Annex I and shall include exposure scenarios and exposure estimations for the registered substance. The exposure assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards. Annex I, section 6 of the REACH Regulation requires you to characterise the risk for each exposure scenario.

In the present case you have provided 9 exposure scenarios (ES) describing 9 identified uses: ES1) Manufacture; ES2) Formulation coatings, inks, adhesives; ES3) Use at industrial site in coatings; ES4) Use at industrial site in printing inks; ES5) Use at industrial site as heat transfer fluids; ES6) Professional use in coatings; ES7) Consumer use in coatings; ES8) Service life (consumers) indoor use; ES9) Service life (consumer) outdoor use.

Pursuant to Annex I, section 5.1.1 of the REACH Regulation, exposure scenarios (ES) shall include, where relevant, a description of operational conditions (OCs) and of risk management measures (RMMs). As indicated in Annex I, section 5.2.2. of the REACH Regulation, emission estimation shall be performed under the assumption that the risk management measures and operational conditions described in the exposure scenario have been implemented. These RMMs and OCs should be included in the exposure scenarios provided in the CSR.

As stated in the *Guidance on information requirements and chemical safety assessment* Chapter R.16: Environmental Exposure Estimation (ECHA, version: 3.0, February 2016) both OCs (*a set of actions, tools, parameters such as amount of substance, process temperature and pH, duration and frequency of release, type of use (e.g. indoor or outdoor), containment of process (open or closed), continuous or batch process (leading to an intermittent release), capacity of surroundings, etc.*) and RMMs (e.g. *filters, scrubbers, biological or physico-chemical wastewater treatment plants etc.*) have an impact on the type and amount of release and the resulting exposure. ECHA guidance R.16 specifically provides default release factors associated with different Environmental Release Categories (ERCs). These default release factors can be used for a first tier assessment of the emissions. However, better information may be available that could then be used instead. In particular, release factors can be refined by taking into account RMMs and OCs. In this case, it is important to explicitly link such RMMs and OCs to the release factors and communicate them properly to the downstream users in the exposure scenarios. For example, sector specific environmental release categories (spERCs) developed by industrial sector organisations can be used in place of the conservative default ERCs of ECHA's guidance R.16. However, spERCs have to be linked to the applied RMMs and OCs driving the release estimation and that shall be described in the exposure scenarios.

ECHA notes that you have used such SpERCs in order to estimate exposure for ES2, ES3, ES4 and ES5. ECHA further notes that for ES4 you have deviated from the SpERC used (i.e. CEPE SpERC 5.1a.v1) since you have used an air release of [redacted]% when the SpERC sets this release to 2% with the following justification: "*fraction of CEPE SpERC 5.1a.v1 (2%) is reduced as spraying process is totally enclosed proceeding in special equipment with no substance release to air. Overspray is recovered within the enclosement and reused*". However, ECHA highlights that the deviation from the SpERC used is not justified since you have not explained the conditions under which the SpERC is built upon. Therefore ECHA is not able to evaluate how those relate to your process. More specifically, you state that the spraying process is in a closed system but you have not described any risk management measure suggested by the SpERC used to understand whether or not it covers this exposure scenario (e.g. wet scrubber? filtration?).

ECHA also notes that for ES1 you have used release factors of [redacted]% with the following justifications: "*waterfree production process, closed system, no contact of substance with water (information of manufacturer)*", "*production in closed system, exhaust air is incinerated (information of manufacturer)*", "*according to the manufacturer, no release of sludge to soil (information of manufacturer)*". This is a deviation from the default worst case scenario set in ECHA Guidance R.16 (i.e. 5% to air, 6% to water before STP and 0.01% to soil) and it is insufficiently justified to enable verification. More specifically, the justifications rely on the enclosure of the process but, however, breakage of the integrity/enclosure of the system could be expected considering that some contributing scenarios are described with process categories with potential for release, i.e. transfer of substance from/to vessels/large containers at dedicated facilities (PROC 8b), transfer of substance into small containers (dedicated filling line, incl. weighing) (PROC 9), use as laboratory reagent (PROC 15). In addition, cleaning and maintenance activities have not been considered at all for this scenario.
Thus, ECHA considers that the clear and detailed justification (e.g. based on RMMs and/or OCs and/or substance properties) for using other than default ERC release factors in exposure estimation which would comply with Annex I, Section 5.2.2. of the REACH Regulation as further specified in the above referred ECHA Guidance is not provided in the CSR.

Therefore, pursuant to Article 41(1) and 41(3) of the REACH Regulation you are requested to use default release factors and other recommendations of ECHA Guidance R.16 and revise the risk characterisation accordingly for ES1 and ES4 *or* provide a detailed justification (e.g. based on RMMs and/or OCs and/or substance properties) for not using the default release factors as recommended in ECHA Guidance R.16 for estimation of environmental exposure. The chemical safety report shall be amended accordingly.

Appendix 2: Procedural history

You were initially notified that the draft decision does not take into account any updates of your registration after the date when draft decision was notified to you under Article 50(1) of the REACH Regulation. Exceptionally, based on your comments on the draft decision and related information provided in the updated dossier, ECHA has taken into account the relevant updated information, including the updated tonnage band. [redacted]

The compliance check was initiated on 20 November 2015

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and amended the request(s).

ECHA took into account your comments and your updated information of submission number: [redacted]. This has resulted in the removal of the following decision requests: *in vitro* gene mutation study in bacteria; sub-chronic toxicity study (90-day);pre-natal developmental toxicity study in second species; identification of DNELs and risk characterisation; amendment of the following decision requests and modified in Appendix 1: pre-natal developmental toxicity study in first species; extended one-generation reproductive toxicity study in rats; and modified following decision requests in Appendix 1 only: Exposure assessment and risk characterisation for human health (Annex I, Sections 5. and 6.).

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-55 written procedure 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.