EUROPEAN CHEMICALS AGENCY

Helsinki, 31 October 2018

Addressee: [redacted]

Decision number: CCH-D-2114448635-42-01/F
Substance name: 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylindeno[5,6-c]pyran
EC number: 214-946-9
CAS number: 1222-05-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22/12/2015
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

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

2. **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 systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation**

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

You have to submit the requested information in an updated registration dossier by **7 May 2021**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

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

Appendix 1: Reasons

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

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

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

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

However, there is no information provided for a pre-natal developmental toxicity study in a second species. Furthermore, the technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

The available OECD TG 414 study indicated some foetal toxicity that cannot be considered secondary to observed maternal toxicity further supporting the need for further investigation of pre-natal developmental toxicity.

In your comments on the draft decision, following the procedure set out in Article 50(1) of the REACH Regulation, you disagree with ECHA's reasoning for requesting pre-natal developmental toxicity study in second species.

You have stated that the observed developmental effects in the pre-natal developmental toxicity study in rat are secondary to maternal toxicity (reduction in maternal body weight). ECHA notes that the reduction in maternal body weight (or body weight gain) is non-dose dependent. The foetal body weight at the high dose level was reduced slightly (by [redacted]) which may have influenced by the lower maternal body weight gain.
Changes in skeletal ossification might be related to smaller foetal weight. However, the vertebral/rib malformations do not seem to be linked to the non dose-dependent reduction of maternal body weight. The foetal findings may not meet the classification criteria but they indicate a concern for developmental toxicity.

You have also stated that "*according to Annex X (and IX) information on developmental toxicity is only needed in one species in the absence of concern and taking all available information into account, and there are no indications that a developmental toxicity test in second species would present a different classification and/or a NOAEL that would drive the risk assessment for this endpoint*". However, the substance subject to this decision is registered at above 1000 tpa (Annex X), and pre-natal developmental toxicity study in second species is a standard information requirement. Therefore, you are required to fulfil this information.

Furthermore, you have stated that in the OECD TG 426 study there were no effects seen in dams and pups up to highest dose (20 mg/kg bw/day) to which clear systemic exposure in foetuses and pups were detected. However, the OECD TG 426 study do not provide equivalent information as OECD TG 414; because the exposure period covers only from late pregnancy until weaning and lacks detailed foetal examination for malformations and variations. In addition, the highest dose tested (20 mg/kg bw/day) is too low (about 50 folds lower than the limit dose) for hazard assessment with respect to developmental toxicity.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.
The test in the first species was carried out by using a rodent species (rat). According to the test method OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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

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

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the 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 provided

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

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

To support your adaptation you have provided the following information:

End point study record 1:

Key study: developmental neurotoxicity, rat, oral (equivalent or similar to OECD TG 426; GLP) with the registered substance, [redacted] 1996 (study report), reliability 2.

Endpoint study record 2:

"Introduction For chemicals produced and/or imported > 1000 ton a two generation rat study may be required to assess the reproductive toxicity for risk assessment (REACH, Annex X, EC, 2007). HHCB is marketed for > 1000 ton and so the reproductive effects need to be fully assessed (ECB, 2008). In the REACH guidance on reproductive toxicity it is also mentioned that the information requirements set out in the REACH annexes should be treated as endpoints rather than studies to be conducted (Chapter R.7A, pg. 369, second paragraph from the bottom (EC, 2008). Therefore all information should be evaluated in a Weight of Evidence (WoE) approach to see if this reproductive toxicity endpoint can be assessed without further animal testing. In the presented waiving statement a WoE is outlined for HHCB to show that for this substance further reproductive toxicity would lead to animal use and costs, without adding further useful information for risk assessment for reproductive effects.

Studies Performed

In the 90-day oral toxicity study on rats of sufficiently high doses (for deriving a dose-response and a (L)NOAEL) and screening for reproductive parameters (enhanced OECD 408) no adverse effects on the reproductive parameters were observed (Api and Ford, 1999b; [redacted] 1996). Besides this test two other in vivo tests were performed. A developmental toxicity test (OECD 414) was carried out and no toxicity was observed ([redacted] 1997, 1999). The maternal and developmental NOAEL was set at 50 and 150 mg/kg bw, respectively. The second study, a peri-postnatal study, was a test in which pups were exposed in utero only and the pups were followed for reproductive effects in the F1 and F2 generation ([redacted] 1997; [redacted] 1996). In this test no reproductive toxic effects were observed at the highest dose tested at >20 mg/kg bw. The overall NOAEL for reproductive effects is therefore >20 mg/kg bw.

In addition to these tests, in vitro assays for HHCB showed very weak estrogenic and anti-estrogenic potency between 0.01 and 10 µMol/l, using a variety of cell lines by various authors ([redacted] 1999, [redacted] 2002, [redacted] 2002;2004;2005a, [redacted] 2005). Marginal repressing effects were also found in vitro on the androgen and progesterone receptor. However, in a vivo test according to the protocol of [redacted] (1987) (referenced in [redacted] 1999) no estrogenic effects were seen in the mouse uterotrophic assay at 50 and 300 mg HHCB in the diet for two weeks.

Conclusion In view of the low toxicity for reproductive effects in all of these tests a two generation study is not warranted.

Literature Review

In addition to the information on HHCB, a recent literature review of [redacted] (2007) demonstrated that well designed 90-day studies, including assessment of reproductive parameters (enhanced OECD 408), could result in:

a) the absence of reproductive effects;

b) the presence of reproductive alerts, which warrant further toxicity testing or

c) would be severe enough for Classification and Labelling.

In addition, the NOAELs of the 90-day study showed no or small differences with the two generation study meaning that for risk characterization the 90-day study would also be sufficiently conservative. Taking this information into account for HHCB, this substance has a well designed 90 day enhanced study that included assessment of the reproductive parameters. Therefore it can be expected that a two generation study would limitedly add to the information on reproductive toxicity for HHCB. In a review of [redacted] (2007), also comparing reproductive effects of 90-day studies with two-generation reproductive toxicity, similar results were seen compared to [redacted]. In the [redacted] review a testing strategy is proposed for those few exception in which the 90-day study would show absence of reproductive toxicity, while reproductive toxicity was present in other studies.

He proposes to carry out a developmental toxicity study after a 90-days study in the absence of reproductive effects. In case this developmental toxicity test was negative in vitro receptor binding assays could be performed to show the reproductive potential. As discussed earlier, we have performed all these assays showing minimal toxicity or activity.

Final Conclusion

The overall information on HHCB for reproductive effects (90-day, developmental toxicity, in utero exposure and F1 and F2 assessment, in vitro and in vivo screening assays on receptor binding) all show low toxicity. This does not warrant further reproductive toxicity testing and C&L. A NOAEL of > 20 mg/kg bw can be derived that can be used for risk characterization. This NOAEL has been shown to lead to the absence of concern in the Existing Chemical regulation assessment (ECB, 2008)".

In addition, you have provided in IUCLID section 8.7.2 a Key study: developmental toxicity, rat, oral gavage (equivalent or similar to OECD TG 414; GLP) with the registered substance, [redacted] 1997; 1999 (study report and publication), reliability 2, with a conclusion that no toxicity was observed in your weight of evidence justification.

Furthermore, you have provided short summary on each experimental studies with regard to *in vitro* and *in vivo* data on "*endocrine interaction*" ([redacted] 1999; [redacted] 2002; [redacted] 2002; [redacted] 2004; 2005a; 2005b; [redacted] 2005).

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

Evaluation approach/criteria

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

ECHA understands from your conclusion of "*(90-day, developmental toxicity, in utero exposure and F1 and F2 assessment, in vitro and in vivo screening assays on receptor binding) all show low toxicity"* that your weight of evidence adaptation justification is based on hypothesis of "low toxicity".

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to an extended one-generation reproductive toxicity study (OECD TG 443) as requested in this decision. ECHA considers that this study provides, in addition to information to general toxicity, information in particular on two aspects, namely on sexual function and fertility in P0 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to pre- and postnatal and adult exposure in the F1 generation and F2 generation until weaning (further referred to as 'effects on offspring').

Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the P0 and F1 parental generations after sufficient pre-mating exposure duration and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood including investigations to detect certain endocrine modes of action, sexual development, and postnatal development of F2 generation. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' needs to be considered.

Furthermore, as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4., Section 4.4 (version 1.1, December 2011), ECHA has evaluated individually your provided sources of information with respect to relevance and reliability and has evaluated the overall provided information for consistency and coverage of the relevant elements as specified above.

Based on the criteria above, ECHA considers the following:

Sexual function and fertility

The available information on sexual function and fertility mainly stems from study similar to OECD TG 426 (females exposed from gestation day 14 to lactation day 21), and from the repeated dose toxicity study (OECD TG 408).

The study similar to OECD TG 426 examined sexual function and fertility of the P0 and F1 generation, however it has many limitations such as: 1) exposure covers only a short period during P0 gestation and lactation, but exposure does not cover premating period, mating and early pregnancy of P0 generation, or any life stages after post-lactation in F1 generation; 2) males are not exposed; 3) only tested up to 20 mg/kg bw/day (no observable adverse effect level, NOAEL, 20 mg/kg bw/day); and 4) many aspects on sexual function and fertility relevant for Annex X, section 8.7.3 are not investigated. Thus, the intrinsic properties of the registered substance cannot be assessed at such low dose level, and according to the conditions specified in the OECD TG 443/OECD TG 426, "*the highest dose level should be chosen with the aim to induce some systemic/maternal toxicity*" and the limit dose is 1000 mg/kg bw/day for oral exposure. In addition, this study addresses only a small part of reproduction and is limited to females only.

Hence, the potential effects on sexual function and fertility were not investigated with appropriate dose level and the investigations are too limited to cover the relevant aspects required in Annex X, Section 8.7.3.

The information from dietary OECD TG 408 study shows no histopathological changes in the major reproductive organs of P0 generation up to 150 mg/kg bw/day, the only parameters related to sexual function and fertility which have been investigated in this study. As the NOAEL is set to the highest dose tested also in this study, it seems that higher dose levels could have been tested specially taking in to account that the 2 weeks range finding study only indicated increased liver weights at 350 mg/kg bw/day. Thus, information from this study has limitation in dose level setting and information related to sexual function and fertility according to Annex X, Section 8.7.3.

In addition, the OECD TG 414 included in your dossier provides information on maintenance of pregnancy but no other information related to sexual function and fertility.

Information on endocrine modes of action is obtained in an extended one-generation reproductive toxicity study. Information on these properties are provided in the dossier from *in vitro* and *in vivo* studies.

- The high IC_{50} value (2.9 µM) for hAR antagonist activity was 5.8 times higher than for flutamide and 29 times higher than for vinclozolin in an assay where repression of transcription of hAR induced by 0.1 nM of dihydrotestosterone was investigated (AR CALUX® cells). The lowest IC_{50} value was for hPR (0.2 µM) being around 41000 times higher than that for the reference substance RU486 in PR CALUX® cells induced by 30 pM of ORG2058. The IC_{50} of 2.4 µM for hERβ was around 3000 times higher than for 4-OH tamoxifen in an assay investigating repression of transcription induced by 0.1 nM E2 in stably transfected HEK293 cells. All these results were published in Schreurs *et al.*, 2005[2] and show only weak or very weak interactions with certain receptors.
- No uterotrophic activity was shown in mice exposed up to 40 mg/kg bw (Seinen *et al.*, 1999[3]).

[2] Schreurs RHMM, Sonneveld E, Jansen JHJ, Seinen W, van der Burg B: Interaction of Polycyclic Musks and UV Filters with the Estrogen Receptor (ER), Androgen Receptor (AR), and Progesterone Receptor (PR) in Reporter Gene Bioassays. Toxicological Sciences 83, 264–272 (2005)

[3] Seinen W, Lemmen JG, Pieters RH, Verbruggen EM, van der Burg B: AHTN and HHCB show weak estrogenic-but no uterotrophic activity. Toxicol Lett 111 (1-2):161-8 (1999)

- In an *in vivo* transgenic zebrafish study, significant repression of 17b-estradiol induced transactivation was observed at test concentrations of 25.8 and 258 µg/L, and 20% was achieved at the highest concentration (Schreurs *et al.*, 2004[4]).

Based on the registration dossier you have indicated that these *in vitro* and *in vivo* studies on hormonal activity have been conducted using the registered substance. However, the composition of the test material are not specified in the publications, except that one publication claims purity of 98% ([redacted] 2002). Thus, there is uncertainty how well the substances studied actually represent the registered substance and how much potential changes in composition have influenced on the results.

In addition, this information does not cover the *in vivo* effects reflecting endocrine modes of actions which are investigated in extended one-generation reproductive toxicity study (such as changes in anogenital distance or nipple retention). Furthermore, the available information on endocrine modes of action does not allow to conclude on sexual function and fertility.

Furthermore, the literature references cited in your adaptation justification ([redacted] 2007 and [redacted] 2007) do not contain information on the registered substance nor do you explain why and how the information on effects on offspring as investigated in an extended one-reproductive toxicity could be replaced or predicted for your substance by results from a 90-day study (OECD TG 408) and *in vitro* receptor assays. Because of the limitations of OECD TGs 426, 408 and 414 studies and hormonal activity measurement conducted, and literature cited, to address the elements of effects on offspring according to Annex X, Section 8.7.3, the information you provided is not sufficient to support your conclusion that the substance does not have a dangerous property with respect to sexual function and fertility.

Effects on offspring

With respect to effects on offspring, you have provided information on indication of developmental toxicity observable during prenatal (OECD TG 414) and/or peri/postnatal developmental period (OECD TG 426) studies.

Information from OECD TG 414 study covers the developmental effects due to prenatal exposure. ECHA notes that contradictory to the claim of no toxicity in weight of evidence justification, the robust study summary describes "*a reduction in foetal body weight (by [redacted]), increased incidences of foetal-skeletal (vertebral/rib) malformations and decreased ossification of sternal centra and metatarsals at 500 mg/kg bw/day*" and reduced maternal body weights on GD 20 by [redacted] at 50, 150 and 500 mg/kg bw/day. These effects indicate mild toxicity to the dams and foetuses.

Information from OECD TG 426 covers the developmental effects due to exposure during the late pregnancy and weaning period. However, information on effects on offspring should cover also the effects due to continuous exposure up to the adulthood, mating, gestation, and further to weaning of the F2 generation. Furthermore, ECHA notes that in the provided OECD TG 426 has been conducted using too low dose levels as indicated above.

[4] Schreurs RHMM, Legler J, Artola-Garicano E, Sinnige TL, Lanser PH, Seinen W, Van der Burg B: In vitro and in vivo antiestrogenic effects of polycyclic musks in zebrafish. Environ Sci Technol 38(4): 997-1002 (2004)

Hence, the potential effects on offspring were not investigated with appropriate dose level and exposure did not cover the necessary life stages.

OECD TG 408 study included in your dossier does not provide any information on effects on offspring.

Information on endocrine modes of action is obtained in an extended one-generation reproductive toxicity study. For the reason specified above, the information you provided is not sufficient to support your conclusion that the substance does not have a dangerous property with respect to effects on offspring.

Conclusion

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2 of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

In your comments on the draft decision, following the procedure set out in Article 50(1) of the REACH Regulation, you indicated that you do not agree on the request to perform an extended one-generation reproductive toxicity study. More specifically, you referred to the OECD TG 426 and OECD TG 414 studies in rat and stated that the NOAEL from the requested study "*will be close to but not be lower than 20 mg/kg bw, and that classification and labelling is not needed. Therefore further information derived from the One generation test will not alter the hazard and risk assessment*". However, for reasons explained already in this section above, the available information on the registered substance are not reliable and/or adequate to cover information on sexual function and fertility, and effects on offspring which are the main aspects covered by an extended one-generation reproductive toxicity study. Information is needed not only for risk assessment (NOAEL derivation) but also for hazard identification for classification purposes. You have not explained in your justification why the aspects of reproduction for which you do not have data but are investigated in an extended one-generation reproductive toxicity study would not meet the criteria for hazard classification. Regarding NOAEL derivation you have not explained why the parameters investigated in an extended one-generation reproductive toxicity study would not be lower than 20 mg kg bw/day.

In addition, you stated that there is no need to look for 'similar substance' in the [redacted] studies since this study shows "*fairly complete picture of the chemical universe the 90-day and developmental toxicity studies are sufficiently covering the reproductive effects*". However, ECHA disagrees with your conclusion because substance specific information is required and unless there is a justification as to why the information on other substances can be applied to the registered substance. Furthermore, as already indicated in this section above, [redacted] conclusion is solely based on information from reproductive organs in repeated-dose toxicity studies. Information in reproductive organs are part of the parameters investigated in extended one-generation reproductive toxicity. However, you have not explained why and how this parameter alone would be sufficient to cover information on reproduction that includes also mating behaviour, conception, parturition,

lactation, survival, development, and sexual maturation.
Justification on why and how this information would suffice for hazard classification and risk assessment purposes. Therefore, information on [redacted] studies are disregarded.

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. 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.

The specifications for the study design

Premating exposure duration and dose-level setting

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

Ten weeks premating exposure duration is required if 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). In this specific case ten weeks exposure duration is supported by the lipophilicity of the substance (log Kow of 5.3) to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.
Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals. The extension is inter alia required, if *"the use of the registered substance is leading to significant exposure of consumers and professionals* (column 2, first paragraph, lit. (a) of section 8.7.3., Annex X) *and if there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure"*.

The use of the registered substance in the joint submission is leading to significant exposure of professionals and consumers because the registered substance is used by professionals in [redacted]) and

consumers in [redacted].

In addition, there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure as the log Kow of the registered substance is 5.3.

The information from indications for endocrine-disrupting modes of action is weak as described above and contains uncertainties in relation to the representiveness of the registered substance. ECHA notes that it is unclear whether the registered substance actually reaches the relevant target cells in relevant concentrations in the *in vivo* situation when considering the weak interaction with hAR and hERβ, in particular because there is currently no indication of endocrine disruptive activity available from *in vivo* studies. However, the limited exisiting *in vivo* information has been conducted using very low dose levels and any potential *in vivo* findings due to endocrine mode of action may have been remained undetected. Thus, it is considered, that although not sufficient alone, the available limited information on weak indications of endocrine modes of action may be considered to further support the inclusion of extension of Cohort 1B in a weight of evidence together with the log Kow value.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure and, as weak but considered supportive data, there are weak indications of modes of action related to endocrine disruption from available *in vitro* study (Schreurs et al., 2005) for the registered substance.

Species and route selection

According to the test method 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) 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.

b) 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 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 systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);

- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section 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.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 2 October 2017.

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

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

ECHA took into account your comments and did not amend the request(s).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Note regarding your general comment on procedure, "ECHA usually notifies the registrant that a compliance check is up coming and ECHA will consider an updated dossier before a certain date. The Lead Registrant (LR) has not received such a notification. This means that the LR has not updated its dossier using its current knowledge on ECHA's interpretations on the REACH regulation e.g. on reporting adaptations to the Annex X in cases where not the exact endpoint is fulfilled". ECHA responded directly to this general comment on procedure via REACH-IT on 15 July 2018, outlining the purpose of the list of substances which may be subject to compliance check; your responsibility as a registrant under Article 22(1) and relevant ECHA REACH guidance on adaptations.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.