EUROPEAN CHEMICALS AGENCY

Helsinki, 13 September 2018

Addressee: [redacted]

Decision number: CCH-D-2114440084-59-01/F
Substance name: Reaction mass of butane-2,2-diyl dihydroperoxide and di-sec-butylhexaoxidane
EC number: 700-954-4
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11/04/2017
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. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce 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;**

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

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

You have to submit the requested information in an updated registration dossier by ***20 July 2021***. You also have to update the chemical safety report, where relevant.

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 Claudio Carlon, Head of Unit, Evaluation E2

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

Appendix 1: Reasons

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

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.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter 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.

In the technical dossier you have provided a study record for a reproduction/developmental toxicity screening test (test method: OECD TG 421), which fulfills the information requirement of Annex VIII, section 8.7.1. This study does not provide the information required by Annex X, Section 8.7.3. because its protocol differs from the OECD TG 443 protocol in many respects, namely it does not cover key elements, such as exposure duration, frequency and type of observations, and the details and number of parameters assessed, life stages and statistical power of an extended one-generation reproductive toxicity study (the number of animals per dose group). More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. Therefore, your adaptation of the information requirement is rejected.

In addition you provided the following justification as an adaptation for the information required according to Annex X, section 8.7.3.: *"According to Annex IX, column 1 of REACH, further testing should be carried for the evaluation of the toxicity to reproduction if adverse effects on reproductive organs or tissues were revealed by the repeated dose toxicity studies (28 day or 90 day) or other data on toxicity to reproduction. The available OECD 408 study (Repeated Dose 90-Day Oral Toxicity) in rats as well as an OECD 421 study (Reproduction/Developmental Toxicity Screening Test) in rats with the substance itself did not indicate such adverse effects [...]. This study was conducted to provide preliminary information on the potential adverse effects of methyl-ethylketone peroxide on male and female reproduction. This investigation encompassed gonadal function, mating behavior, conception, parturition and lactation of the F0 generation and the development of offspring from conception through day 4 of postnatal life. [...]. Based on the results of this study, F0 parental systemic toxicity was observed at 100/75 mg/kg/day as mortality/moribundity, reductions in body weight and food consumption, and macroscopic and microscopic findings*

in the stomach. No signs of parental systemic toxicity were observed at 25 and 50 mg/kg/day; therefore, the no-observed-adverse-effect level (NOAEL) for parental systemic toxicity was 50 mg/kg/day. No effects on F0 reproduction were noted […] therefore the NOAEL for F0 reproductive toxicity was 75 mg/kg/day. […] because mean F1 pup body weights in the 100/75 mg/kg/day group were lower than control values, the NOAEL for F1 neonatal toxicity was 50 mg/kg/day. There were no differences between the vehicle control groups when F0 and F1 parameters were evaluated; therefore, the toxicity observed at the 100/75 mg/kg/day dosage level was due the methyl-ethylketone peroxide and not to the diluent components.

*The objective of the OECD 408 study was to obtain information on the possible health hazards likely to arise from repeated exposure with MEKP at three dose levels over a prolonged period of time (90 days) followed by a 28-day recovery period in order to assess reversibility, persistence or delayed occurrence of potential toxicological effects. The test item was administered orally (by gavage) to […] rats […] at 0 (vehicle control), 150, 50 and 20 mg/kg bw/day doses […] for 90 or 91 days. […] As a result, slight and reversible elevation in the percentage of reticulocytes at 150 and 50 mg/kg bw/day (male and female) along with slight changes in the spleen weight at 150 mg/kg bw/day (male and female) and at 50 mg/kg bw/day (female) were detected […]. Although changes in the percentage of the reticulocytes and spleen weight might be indicative of disturbances in the erythropoiesis, all related parameters remained well within the normal (historical control) ranges and there were no supporting findings referring to red blood cell deterioration or destruction (hematology, clinical chemistry or histopathology), therefore these changes were considered to be not adverse. Based on these observations the No Observed (Adverse) Effect Level (NO(A)EL) was determined to be 150 mg/kg bw/day for male and female animals. Furthermore, the test item was examined for its possible prenatal developmental toxicity [*OECD TG 414*] […] There was no mortality and treatment related clinical signs and necropsy findings in the 65 and 20 mg/kg bw/day dose groups. A slight, but statistically significant reduction in the body weight gain was observed in the food consumption and body weight gain of the dams in the 200 mg/kg bw/day group between gestation days 11 and 17 which was attributed to an effect of the test item. There were no treatment related differences in the food consumption and body weight of the animals in the 65 and 20 mg/kg bw/day groups. The mean number of implantations, intrauterine mortality and sex distribution of the fetuses was not influenced by the treatment. There were no test item related differences in the fetal- and placental weight, body weight retardation and other external, visceral and skeletal variations. There were no fetal malformations found at external and skeletal examination. […] As a conclusion, based on these observations the No Observed Adverse Effect Level (NOAELs) were determined as follows: NOAEL (maternal toxicity): 65 mg/kg bw/day, NOAEL (developmental toxicity): 200 mg/kg bw/day. Based on the above presented data no adverse effects on fertility are to be expected. Further testing would therefore most likely not lead to other results and would in conclusion not improve the hazard assessment of the substance. The available data are considered reliable and sufficient and therefore further testing (extended one-generation reproductive toxicity study) is not required and will not be carried out also taking animal welfare reasons into account. "*

While you have not explicitly claimed an adaptation according to Annex IX, Section 8.7.3, column 1, you have provided information that could be interpreted as an attempt to adapt the information requirement of Annex X, Section 8.7.3, column 1 with available information. Thus ECHA has considered if the available information meets the specific rules for adaptation in Annex X, Section 8.7, column 2, or general rules for adaptation according to weight of evidence adaptation at Annex XI, Section 1.2.

ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7., column 2 because the registered substance is not known to be a genotoxic carcinogen or a germ cell mutagen; it is not of low toxicological activity, since some effects are observed in the repeated dose toxicity studies and, thus, there is also systemic absorption, and you have not demonstrated no or no significant human exposure (e.g. PROC 8a for professional use of reactive substances or PC1: wide dispersive indoor use of reactive substances, mixing and loading). Finally it does not meet the criteria for classification for reproduction as category 1A or 1B (H360F), and it is not known to cause developmental toxicity.

The information you have provided could be also interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your arguements with respect to this adaptation.

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 as insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific intrinsic properties of the registered substance with respect to an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study provides, in addition to information on 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 (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 parental (P0) generation after sufficient pre-mating exposure duration and histopathological examinations of reproductive organs in both P0 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 and sexual development. 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 the sources of information you provided, with respect to relevance and reliability and has evaluated the overall provided information for consistency and coverage of the relevant elements as specified above.

You have provided information from four separate studies according to following OECD TGs: OECD TG 421, OECD TG 407, OECD TG 408, and OECD TG 414. Based on the criteria above, ECHA considers the following:

Sexual function and fertility

The available information on sexual function and fertility stem from the submitted reproductive toxicity studies:
As explained above the protocol of the OECD TG 421 study differs from the OECD TG 443 protocol in many respects, namely it does not cover key elements, such as exposure duration, frequency and type of observations, and the details and number of parameters assessed, life stages and statistical power of an extended one-generation reproductive toxicity study (the number of animals per dose group), at least 20 pregnant females per group. Certain relevant investigations, such as functional fertility after a 10-week premating exposure to cover spermatogenesis and folliculogenesis before mating, histopathology of the reproductive organs in F1 animals in adulthood, sexual maturation, oestrous cycle measurements in F1 animals, and investigations related to hormonal modes of action are not included in OECD TG 421. Furthermore, you did not provide information on sperm parameters in P and F1 generations.

ECHA notes that information from an OECD TG 408 study cannot be considered as an adaptation to the OECD TG 443 study, since it only provides information on histopathological findings in reproductive organs but does not cover any other elements on sexual function and fertility including mating behaviour, conception, pregnancy, parturition, and lactation in the parental generation after 10 weeks pre-mating exposure duration. The same deficiencies apply to the OECD TG 407 study.

Investigations according to OECD TG 414 inform only on pregnancy maintenance to some extent but not on any other relevant elements for sexual function and fertility.

Additionally, ECHA considers that the doses and vehicles selected in some of the studies provided may not be appropriately chosen. ECHA also notes that three different rat strains have been used in different studies. This inconsistency in approaches may reduce the possibility for an independent and reliable interpretation of the toxicological properties of the registered substance.

In combining all repeated dose toxicity studies, screening reproductive and developmental toxicity studies, the information you provided does not adequately address all relevant elements with respect to sexual function and fertility.

Effects on offspring

ECHA notes that your adaptation justification does not adequately address the effects on offspring. The information provided does not inform on the key elements which need to be investigated in this regard. The OECD TG 421 screening study investigates development and offspring toxicity only until postnatal day 4, not until adulthood with relevant parameters. ECHA notes that information from an OECD TG 414 study cannot be considered as an adaptation to the effects on offspring according to OECD TG 443 study, because it only provides information on effects observable pre-natally and not effects on offspring observable and/or due to postnatal exposure up to adulthood.

Conclusion

Hence, of the information you provided to support your adaptation, none of the individual pieces available (sub-chronic toxicity study, screening study, and pre-natal developmental toxicity study) provides adequate coverage of the key parameters of an extended one-generation reproductive toxicity study, considered either individually or taken together. Consequently ECHA cannot conclude whether the substance has a particular 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 you indicated your disagreement with the study request and you confirmed your intention to adapt this standard information requirement according to Annex XI, Section 1.2.

Firstly ECHA notes that the extended one-generation reproductive toxicity study (EU B.56; OECD TG 443) is a standard information requirement at REACH Annex X level. Secondly, as already explained above, under this section of the decision, the adaptation cannot be accepted since the available studies (sub-chronic toxicity study, screening study, and pre-natal developmental toxicity study) cannot be considered as being "*sufficient*", as you claim, to draw a conclusion on this standard information requirement.

Also, in your comments you state that there are "*no concerns based on available data*", "*no indication that the substance could affect reproduction*" and "*no adverse effects on fertility are to be expected*". Though you do not explicitly indicate in your comments, ECHA considers this information as an attempt to waive the study on the basis of "*low toxicological activity*" according to Annex X, Section 8.7, column 2. However, as already explained above, ECHA notes that there is evidence of toxicity with the registered substance, hence, the adaptation (Annex X, Section 8.7, column 2) cannot be fulfilled since none of the adaptation criteria are met.

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

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

b) The specifications for the study design

Premating exposure duration

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

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). In addition, the registered substance is not stable on its own and is used with solvents and stabilitisers as you stated: "*Methyl-ethylketone peroxide is stable in Diacetone alcohol (DAA), 2,2,4 -trimethyl-1,3 -pentandiol-isobutyrat (TXIB) and dimethyl phthalate (DMP) as those are used as stabilising agents. The solvents were assigned to diluting agents typ A (according to definition 2.5.3.5.2 "UN Recommendations on the Transport of Dangerous Goods") and are considered as suitable diluting agents for methyl-ethylketone peroxide".*

In your comments on the draft decision you agreed with the proposed study design, if the extended one-generation reproductive toxicity study is requested however, you disagreed

with the ten weeks premating period. You claimed that according to the OECD TG 443, "*2 weeks are sufficient*". Moreover you state that "*ECHA fails to justify a prolongation to 10 weeks based on the data available already for the substance* [...]". ECHA notes that according to the OECD TG 443 the parental generation should be dosed for a defined pre-mating period selected on the basis of available information for the test substance, but for a minimum of two weeks. For this specific case, as already explained above, according to the ECHA Guidance document (R.7a, chapter R.7.6.2.2.3, p. 475-7, version 6.0, July 2017), as a starting point, ECHA is requesting a ten week premating exposure duration since you did not provide any substance-specific justifications to support a shorter premating exposure duration.

Dose-level setting and species

ECHA draws your attention to the fact that the highest dose level shall aim to induce 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. ECHA notes that you have conducted several studies with different solvents and different rat strains.

In the OECD TG 421 study, Sprague Dawley rats were dosed by gavage, at doses 20, 50, 100 mg/kg/day, in 0.1 % polysorbate 80 (as solvent). No toxicity was reported, apart from slight impact on body weight gain, which was not considered adverse.

ECHA notes that the solvent used in the short-term repeated dose toxicity OECD TG 407, in Fisher 344 rats, (oral route, gavage) was corn oil (with doses of 0, 20, 65, 200 mg/kg/day) and that you reported a NOAEL of 200 mg/kg/day since "*no test item related adverse effects [were] observed.*" You concluded that "*trend for reduced feed consumption was observed in both sexes in the high-dose groups. At least in the high dose groups the connection between reduced feed consumption and reduced body weight [gain] was obvious*".

In the provided OECD TG 414 in Wistar rats (oral route, gavage) the vehicle was sunflower oil (with doses of 0, 20, 65, 200 mg/kg/day) and you reported that "*[t]here was no mortality and treatment related clinical signs and necropsy findings in the 65 and 20 mg/kg bw/day dose groups [except a] slight, but statistically significant reduction in the body weight gain [...] of the dams in the 200 mg/kg bw/day group between gestation days 11 and 17 which was attributed to an effect of the test item.*"

In the OECD TG 408 study, Wistar rats were dosed at 20, 50 and 150 mg/kg bw/day (gavage) and the solvent used was sunflower oil. This led the top dose (150 mg/ kg bw/day) to not produce any adverse effects, as the "*NO(A)EL was determined to be 150 mg/kg bw/day for male and female animals*". ECHA acknowledges that you indicated that the dose selection was based on a study performed according to the OECD TG 407.

If adequately conducted, the OECD TG 408 gives amongst others an indication of reproductive effects to allow for the identification of chemicals with the potential to cause reproductive organ effects, which may warrant further in-depth investigation. However, ECHA questions your choice of the doses for the OECD TG 408 you submitted, where it is expected that "*The study [...] provides information on the major toxic effects, indicate target organs and the possibility of accumulation, and can provide an estimate of a no-observed-adverse-effect level of exposure which can be used [...] for establishing safety criteria for human exposure.*" Furthermore, "*Unless limited by the physical-chemical nature*

or biological effects of the test substance, the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering." As the NOAEL has been set to the top dose, it indicates that you/the authors did not consider the findings at that dose level or at lower dose levels as adverse. However, the NOAEL for the range finding study (OECD TG 407) was set at 200 mg/kg bw/day based on no adverse effects at the highest dose investigated. You have not convincingly explained why it was considered necessary to select a lower top dose of 150 mg/kg bw/day for a repeated dose (90-day) study. Furthermore, ECHA notes that there are dose-related findings in the 90-day study which have been considered as of no toxicological value because they are within historical control values. However, the relevance and adequacy of the historical control values for the case are not presented.

Taking into account the inapproriate dose level selection in many previous studies, not meeting the aim to induce toxicity but not death or severe suffering at the highest dose level, ECHA recommends that you consider conducting a separate dose finding study before performing the extended one-generation reproductive toxicity study. ECHA also notes that you have used various solvents in previous studies which also influence the results. ECHA considers that oil (sunlfower or corn) is an appropriate solvent and that testing should be performed with oil. It is also recommended that you report the results of the range finding study or studies with the main study. This will support the justifications of the dose level selections for the requested extended one-generation reproductive toxicity study and an appropriate interpretation of its results.

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats. The OECD TG 443 also specifies that "*strains with low fecundity or a well-known high incidence of spontaneous developmental defects should not be used*". Useful information regarding an appropriate strain may be found in the OECD GD 116.

Route selection

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

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce 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.

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: (i) length of the premating exposure duration and dose level selection; (ii) reasons as to why

Cohort 1B was extended or not; (iii) termination time for F2 generation; and (iv) reasons as to why Cohorts 2A/2B and/or Cohort 3 were included or not.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, 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 the extension of Cohort 1B, 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. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

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

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.
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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex X, Section 8.7.2., column 2. Indeed you have a provided the following justification: "*The test substance MEKP is registered in a tonnage band over 1000. Pursuant to Article 40(3)(a) and Annexes IX and X of the REACH Regulation, prenatal developmental toxicity studies are part of the standard information requirements to be provided by a registrant. Furthermore, assessment of developmental toxicity has to be done taking two OECD 414 studies performed on a rodent and a non-rodent species (rabbit recommended) into account (Annex X, 8.7.2 of the REACH Regulation). [...] Taken together the available data, there is no indication of the test substance inducing any adverse effects concerning development. To meet the requirements of REACH, assessment of developmental toxicity has to be done on the basis of two OECD 414 studies conducted on a rodent and a non-rodent species. However, conducting a second OECD 414 study does not seem necessary as a reliable pre-natal developmental toxicity study conducted with rats as the standard species is already available and there is no indication of adverse effects with regard to developmental toxicity, even at toxic doses. Therefore, and for animal welfare reasons, the second OECD 414 study does not seem justified.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7., column 2 because the registered substance is not known to be a genotoxic carcinogen or a germ cell mutagen; it is not of low toxicological activity, since

some effects are observed in the repeated dose toxicity studies and you have not demonstrated no or no significant human exposure (e.g. PROC 8a for professional use of reactive substances or PC1: wide dispersive indoor use of reactive substances, mixing and loading). Furtheremore it is not meeting the criteria for classification for reproduction as category 1A or 1B (H360D). While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation. However, none of the individual pieces of information available (sub-chronic toxicity study, screening study, and pre-natal developmental toxicity study) provide adequate coverage of the key parameters of a prenatal developmental toxicity study performed in a non-rodent species, either individually, or taken together. Neither have you provided any substance-specific information on species difference regarding prenatal developmental toxicity which could allow to conclude on the hazardous properties for developmental toxicity.

Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision you indicate that the pre-natal developmental toxicity study in a second species cannot be requested "*for the only sake of formal fulfilment of information requirements*" as "*vertebrate animal testing is considered neither scientifically nor legally justified*". ECHA notes that this substance is registered at REACH Annex X level, hence a prenatal developmental toxicity study conducted on a second species is a standard information requirement in addition to the prenatal developmental toxicity study in a first species (which is already available in the technical dossier) that is required at REACH Annex IX level. According to the ECHA Guidance document (R.7a, chapter R.7.6.2.3.2, p. 490, version 6.0, July 2017) the availability of information on two species allows a more comprehensive evaluation of prenatal developmental toxicity. ECHA notes that in your comments you confirmed your intention to adapt this standard information requirement according to Annex XI, Section 1.2. However, as already indicated above, under this section of the decision, the adaptation cannot be accepted. Moreover, in your comments you indicate that from the available data with the registered substance there is no indication that "*the substance could induce significantly different species specific effects on endpoints of prenatal developmental toxicity*." However, you failed to provide any substantiated evidence to support this statement.

In your comments you also claim that the substance belongs to the group of organic peroxides which have already been "*handled under rigorous conditions*" hence additional information on the registered substance "*would not result in any further risk management measures in practice*". However, you failed to provide any substantiated justification, including a read-across justification on why ECHA should consider this data on organic peroxides, if available, to cover this standard information requirement. 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 EU B.31./OECD 414, the rabbit is the preferred non-rodent species and the rat is the preferred 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) R.7a,

chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route. Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route.

Note for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 40 months. You sought to justify this request (i.) since you intend to undertake the requested tests in a sequential manner; and (ii.) due to limited laboratory capacity, where you also provided a supporting statement from the testing laboratory. ECHA notes that both studies requested in the decision can be initiated at the same time hence the timeline cannot be extended for this reason. As regards the laboratory capacity issue, ECHA understands that the testing laboratory has limited capacity at the time being and that the studies can only be initiated in 2019. ECHA has considered the timeline of the decision making process for this compliance check decision and has only partially granted the request and set the deadline to 34 months.

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 14 March 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 requests and amended the deadline.

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

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

Appendix 3: Further information, observations and technical guidance

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

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

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

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

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