~~Confidential~~

Helsinki, 09 March 2022

Addressees
Registrant(s) of JS_DGEBADA_55818-57-0 as listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject to this decision
7 May 2020

Registered substance subject to this decision ("the Substance")
Substance name: 4,4'-Isopropylidenediphenol, oligomeric reaction products with 1-chloro-2,3-epoxypropane, esters with acrylic acid
EC number: 500-130-2

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By the decision of 24 October 2017 ("the original decision") ECHA requested you to submit information by 31 October 2019 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 ("the REACH Regulation"), ECHA examined the information you submitted with the registration dossier specified in the header above, and concludes that

Your registration still does not comply with the following information requirement:

A. Information required from all the Registrants subject to Annex X of REACH

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in Wistar rats, oral route with the registered substance specified as follows:

   -Ten weeks premating exposure duration for the parental (P0) generation;

   -Dose level setting shall aim to induce some toxicity at the highest dose level;

   -Cohort 1A (Reproductive toxicity);

   -Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;

   -Cohorts 2A and 2B (Developmental neurotoxicity); and

   -Cohort 3 (Developmental immunotoxicity).

You are therefore still required to provide this information requested by the original decision.

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annexes X of REACH".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They have the duty under Articles 125 and 126 of Regulation No 1907/2006 to ensure that the requests in the original decision are enforced and complied with and, to that end, inter alia, to carry out checks and impose effective, proportionate and dissuasive penalties[1].

Authorised[2] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] See paragraph 143 of the judgment of the European Court of Justice of 21 January 2021 in Case C-471/18 P Germany v Esso Raffinage.

[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 A: Reasons to request information required under Annex X of REACH

1. Extended one-generation reproductive toxicity study

You were requested to submit information derived with the Substance for Extended one-generation reproductive toxicity (EOGRT) study (EU B.56/ OECD TG 443) in Wistar rats, oral route with 10-week premating exposure, dose levels that shall aim to induce some toxicity at the highest dose, Cohorts 1A and 1B without extension, Cohorts 2A and 2B, and Cohort 3.

In the updated registration subject to follow-up evaluation, you have provided an oral (gavage) EOGRT study ([redacted], 2020) according to OECD TG 443 in Wistar Han rats, performed with the Substance, and including Cohorts 1A and 1B without extension, Cohorts 2A and 2B, and Cohort 3. The P0 animals were exposed for 10 weeks before mating. The doses used in the study were 0, 40, 100 and 200 mg/kg bw/day.

We have assessed this information and identified the following issues:

As further explained below, the EOGRT study is rejected as being not compliant because

- selected dose levels were too low, *i.e.* the highest dose level did not produce toxic effects and the evidence you provided for dose selection rationale does not demonstrate that the aim was to induce some toxicity at the highest dose, and
- the results of the T-cell dependent antibody response (TDAR) assay in Cohort 3 are not reliable.

Furthermore, the results show a concern for endocrine activity, sexual function, fertility and development (see below), but no conclusion on endocrine properties and classification and labelling for reproductive toxicity in accordance with the CLP Regulation can be made due to too low dose level selection. Thereby the study is inconclusive for hazard assessment.

You have submitted comments on the draft decision. In your comments you consider that the dose-level selection of the conducted EOGRT study is appropriate and that no alerts for endocrine activity are seen in the OECD TG 443, 422, 408, and 414 studies. You explain that a repeat of the study for risk assessment, classification and labelling purposes is not justified, the results of the TDAR are acceptable, and that the high animal cost needs to be considered. You conclude that repetition of the study is not required. In your comments you also consider that the decision is based on a completeness check. However, this decision is a compliance-check decision.

In the following ECHA sets out its reasons for concluding on the incompliance of the information that you submitted in the updated registration dossier in response to the original decision. Because of all the detail provided in your comments on the initial draft of this decision, these specifics are addressed under separate headers at the end of the sections related to the (a) dose level selection and (b) TDAR reliability as well as in a new section (c) relating to your comments on the requirement of an EOGRT study under Annex IX to REACH.

a) Dose level selection

Requirements for the dose selection

The objective of the study is to demonstrate if the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under Regulation (EC) No 1272/2008 ("the CLP Regulation") apply for the Substance, if the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification

of appropriate risk management measures in the chemical safety assessment (see OECD TG 443, paragraph 22; OECD GD 151, paragraph 27/28; Section 1.0.1 of Annex I of the REACH Regulation; and Recital 7 to Regulation No 2015/282).

To investigate sexual function and fertility for these purposes, the highest dose level must be determined based on clear evidence of an adverse effect on sexual function and fertility, but no deaths[3] or severe suffering such as persistent pain and distress[4] in the P0 animals (see also OECD TG 443, paragraph 21).

With regard to dose selection, the original decision accordingly explained that "*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.*" [5].

The ECHA Guidance further explains that "*for fertility as well as developmental toxicity it is important to investigate whether these reproductive toxicity effects are considered to be a secondary non-specific consequence of other toxic effects seen, such as, maternal toxicity, which may occur at the same dose level as the reproductive effects. However, in general, all findings on reproductive toxicity should be considered for classification purposes even if they are seen in the presence of parental toxicity. A comparison between the severity of the effects on fertility/development and the severity of other toxicological findings must then be performed. Thus, it is important to get information about the reproductive toxicity profile of a substance including the spectrum of reproductive toxicity effects related to different dose levels as well as information to allow evaluation of the potency for reproductive toxicity of a substance. Therefore, the highest dose level should be intended to produce some toxicity to provide adequate information on reproductive toxicity for the purpose of both classification (including categorisation within the Reproductive toxicity hazard class) and risk assessment. For further information and clarification see the CLP criteria for classification (Section 3.7, Annex I of CLP) and Section 3.7 in the Guidance on the Application of the CLP criteria.*"[6]

To conclusively assess the tested parameters in the EOGRT study, the doses need to be sufficiently high to be able to conclude that the Substance does not cause reproductive effects on the tested parameters when clear evidence of such toxicity is not observed (Section 11.1.1 of Annex II, REACH). In the CLP Regulation there is no specific limit dose above which no classification is anymore justified if reproductive effects are seen, but there is a reference to a concept of such a limit dose and a statement that some guidelines for test methods specify a limit dose (see CLP 3.7.2.5.7 and 3.7.2.5.9).

In OECD TG 443 the limit dose is 1000 mg/kg bw/day when human exposure does not indicate the need for a higher dose level. Section 3.7.2.5.7 in Annex I to the CLP Regulation also acknowledges that establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model. In accordance with Section 3.7.2.5.8 in Annex I to the CLP Regulation, in principle adverse effects on reproduction seen only at very high dose levels in animal studies (*e.g.* doses that induce prostration, severe inappetence, excessive mortality) would normally not lead to classification unless other information is

[3] For that purpose, 'no deaths' means no more than 10% mortality (Section 3.7.2.4.4 of Annex I to the CLP Regulation).
[4] OECD GD 19, paragraph 18.
[5] The original decision, page 7. See also REACH Guidance, R.7a, R.7.6.2.2.3, which states that "*… as a starting point, a highest dose level with the aim to induce some toxicity for all variant study designs of an extended one-generation reproductive toxicity study should be proposed*" and footnote 121 explains that "*The … dose selection should be appropriate to meet risk assessment and classification and labelling purposes as required by Regulation (EC) No 1907/2006 and Regulation (EC) No 1272/2008 of the European Parliament and of the Council.*" Table R.7.6–2 states that "*highest dose level must be chosen with the aim to induce some toxicity.*"
[6] ECHA Guidance R.7a, R.7.6.2.3.2, Stage 4.1 (vi) on Dose level selection.

available, *e.g.* indications that humans may be more susceptible. Therefore, the limit dose of 1000 mg/kg bw/day given in the OECD TG 443 is not a specific limit dose above which reproductive effects should be considered to be outside the criteria for classification.

To conclude, there needs to be some toxicity at the top dose, or a top dose of (at least) 1000 mg/kg bw/day (*i.e.* the limit dose given in the OECD TG 443) must be used. Some toxicity comprises either reproductive toxicity providing clear evidence of such effects in the tested parameters or other toxicity (*e.g.* in maternal animals), that is sufficiently severe but not causing *death or severe suffering* that would invalidate the use of reproductive effects at the same dose level for classification and labelling.

Your dose selection rationale

You explain that the dose selection for the main OECD TG 443 study was based on "*the results of previously conducted (repeated and reproduction) toxicity studies with oral exposure of DGEBADA in rats*"; *i.e.* a reproductive/developmental toxicity screening study according to OECD TG 422 in Sprague-Dawley rats with dose levels of 0, 100, 300 and 900 mg/kg bw/day, a prenatal developmental toxicity study according to OECD TG 414 in Wistar Han rats with dose levels of 100, 300 and 1000 mg/kg bw/day, and a 90-day toxicity study according to OECD TG 408 in Wistar Han rats with dose levels of 100, 300 and 1000 mg/kg bw/day. You conclude that "*based on adverse effects observed in the 90-day repeated toxicity in which no NOAEL was established (LOAEL = 100 mg/kg/day), dose levels were selected to be 40, 100 and 200 mg/kg/day in an attempt to produce graded responses to the test item. The high-dose level should produce some toxic effects, but not death nor obvious suffering. The mid-dose level was expected to produce minimal to moderate toxic effects. The low-dose level should produce no observable indications of toxicity.*"

The OECD TG 422 and 414 studies showed absence of adverse effects in parental animals and offspring up to the top dose of 900 and 1000 mg/kg bw/day, respectively. These studies in the context of dose selection are valuable to demonstrate the tolerable doses by parental animals and offspring. The results of the OECD TG 422 and 414 studies suggest that pregnant and paternal animals seem to tolerate well doses at around 1000 mg/kg bw/day.

In the OECD TG 408 study, effects were observed particularly on clinical signs (incidental salivation), body weight (test-item related reduction of mean body weight in high-dose males within the range of typical variation), haematology in males and/or females (effects on platelet, neutrophile, and monocyte counts), clinical biochemistry in males and females (increased cholesterol and phospholipid levels, reduced glucose, potassium, protein, and globulin levels, hepatic enzyme activation), behaviour in males and females (effects on grip strength and locomotor activity), organ weights (reduced prostate weights without histopathological correlates, increased mean relative kidney weights, reduced absolute and relative mean thymus weights), histopathology (minimal decreased number of lymphocytes in the mesenteric lymph nodes, slight tubular vacuolation in kidneys, minimal focal/multifocal hepatocellular necrosis, minimal multifocal cell hypertrophy in the pituitary), and seminology (decreased progressive sperm cells, increased mean number of stationary sperm cells). You derived a NOAEL < 100 mg/kg bw/day based on behaviour (functional findings), clinical biochemistry and organ weights and organ / body weight ratios (prostate). Therefore, you considered the findings leading to a NOAEL as adverse toxic effects.

Based on the findings from the OECD TG 408 study at 100 mg/kg bw/day (effects on grip strength and locomotor activity, clinical biochemistry, and prostate weight) and above, you selected a top dose of 200 mg/kg bw/day (corresponding to 20% of the limit dose of 1000 mg/kg bw/day) for the OECD TG 443 study.

Findings in the EOGRT study

i. No adversity observed

The following effects were observed in the EOGRT study, which applied a top dose of 200 mg/kg bw/day (*i.e.* 20% of the limit dose):

- Increased mean precoital interval together with a shift to mating at later time points in P0.
- Delayed sexual maturation in F1 (i.e. vaginal opening and achievement of first oestrus and time to first oestrus) with unclear dose response relationship.
- Dose-related incidence of breathing rales at mid and high dose in F1, primarily during the first two weeks of treatment.
- Increased average response amplitude (blocks 1-4), max response amplitude (block 1) and latency to max response (block 1) in high-dose Cohort 2A males.
- Thyroid:
    - Dose-dependent trend to higher TSH values (compared to controls; without statistical significance) in P0 males, which was not seen in P0 females.
    - Dose-dependent trend to slightly higher T4 values (compared to controls; statistically significant at high dose) in P0 males, which was not seen in P0 females.
    - No effect on TSH levels and a dose-dependent trend to slightly higher T4 values (compared to controls) in both F1 males and females.
    - Dose-dependent increase in absolute and relative thyroid weights in F1 pups of Cohort 1A, not confirmed in Cohort 1B.
    - No effects on thyroid histopathology.
- Absolute decrease of -11% in adrenal weights compared to controls with statistical significance and relative decrease of -12% compared to controls with statistical significance in high-dose F1 males of Cohort 1A in the absence of macroscopic correlates. This decrease in adrenal weights was not confirmed in Cohort 1B and was also not seen in P0 animals.
- Slight increase of cholesterol levels in mid and high-dose animals without histopathological correlates; the means remained within the internal control range.

You only derived the following effect levels based on the results in the EOGRT study:

- A NOEL value of 40 mg/kg bw/day for F1 offspring (pup) toxicity based on breathing rales and increased cholesterol levels;
- A LOEL value of 40 mg/kg bw/day for P0 male general/systemic toxicity based on decreased TSH levels in P0 males.

You did not identify any NOAEL value, *i.e.* the NOAEL values are higher than the top dose of 200 mg/kg bw/day. Therefore, none of the observed effects are considered adverse because no adverse effect levels such as NOAELs or LOAELs were identified.

ECHA agrees with your conclusion that none of the observed effects are adverse.

ii. Concern for endocrine activity in the EOGRT study not addressed

As explained above, the results of the EOGRT study indicate effects on sexual function and fertility in P0 females (increased precoital interval and shift of mating to later time points, reduced mating index at top dose) and sexual maturation in F1 females (delay of vaginal opening and achieving first oestrus as well as increased time to first oestrus).

With respect to sexual function and fertility of P0 females, an increase of mean precoital interval from 2.8 days in controls to 3.8 days in low and mid dose and 3.2 days in high dose

was observed. Furthermore, most females mated within 5 days but in low, mid and high dose a shift to mating on days 13-14 occurred (*i.e.* at the end of the mating period). Furthermore, 2 females in the high dose group did not mate during the 2-week mating period (mating index = 92% in high dose females) and therefore it can be assumed that there is a shift beyond day 14 of the mating period.

With respect to sexual maturation of F1 female pups, a delay of vaginal opening was observed for all F1 females (i.e. in Cohorts 1A, 1B, 2A and 3). At high dose, vaginal opening was delayed with statistical significance (30.5 days at high dose vs 29.1 days in controls). At low and mid dose, vaginal opening occurred also delayed to 29.9 days and 29.7 days, respectively. Furthermore, achieving first oestrus was delayed with statistical significance at high dose (34.6 days at high dose vs 32.5 days in controls). At low and mid dose, achieving first oestrus was also delayed to 33.2 and 33 days, respectively. Also, time to first oestrus increased but without achieving statistical significance (3 days in controls, 3.4 days at low dose, 3.1 days at mid dose, and 4 days at high dose).

Furthermore, the Substance contains a Bisphenol A core structure. Bisphenol A is a substance, which has been identified as endocrine disruptor and it has a harmonised classification and labelling as Repr. 1B, H360F.

The observed effects on sexual function and fertility of P0 females and on sexual maturation of F1 females together with the structural analogy to Bisphenol A, raises a concern for endocrine activity and reproductive toxicity of the Substance.

However, the too low dose levels do not address the identified concern for endocrine activity.

Conclusion on dose level selection

ECHA agrees with you that the OECD TG 422 and 414 studies showed absence of adverse effects in parental animals and offspring up to the top dose of 900 and 1000 mg/kg bw/day, respectively.

The findings in the OECD TG 408 study are either incidental (salivation), within the range of typical variation (mean body weight changes) or minor even if considered treatment-related (haematology, biochemistry, histopathology). The seminological effects do not result in functional changes as shown in the OECD TG 422 study. You considered that the behavioural effects (functional findings), clinical biochemistry and organ weights and organ / body weight ratios (prostate) are adverse because you derived a NOAEL of <100 mg/kg bw/day based on these.

However, the severity of these effects observed in adult animals at 100 mg/kg bw/day in the OECD TG 408 study does not indicate that the highest possible dose that does not yet cause excessive mortality, prostration or severe inappetence would be at 200 mg/kg bw/day. To the contrary, the findings in the OECD TG 408 study show that higher doses than 200 mg/kg bw/day can be tested in the EOGRT study because these observed effects cannot be considered at all as severe suffering of the test animals; in particular when taking into account that the OECD TG 422 study (*i.e.* a study investigating reproductive toxicity) and the OECD TG 414 (*i.e.* a study investigating developmental toxicity) showed absence of adverse effects in adults and offspring close to (900 mg/kg bw/day) or at the limit dose of 1000 mg/kg bw/day.

In ECHA's opinion, the results of the OECD TG 422, 414 and 408 studies therefore show that there is no indication that selecting a top dose of 1000 mg/kg bw/day would result in severe suffering or death of the test animals and that reproductive toxicity could not be investigated

using that top dose. On the contrary, there were no effects in the OECD TG 422 and 414 studies at 900 and 1000 mg/kg bw/day, respectively.

However, you selected a top dose of 200 mg/kg bw/day for the EOGRT study and this top dose did not result in any adverse effects in the EOGRT study.

Therefore, the dose level selection does not allow the identification of NOAELs and DNELs for risk assessment and it did not demonstrate the aim to induce some toxicity at the highest dose, which would be adequate to fulfil the regulatory requirements for classification and labelling for reproductive toxicity and for identifying substances having endocrine disrupting properties (Article 57(f), REACH). The dose level selection was also not based upon the fertility effects, *i.e.* absence of such effects in the OECD TG 422 and 414 studies.

Therefore, the dose selection does not meet the request in the original decision, the requirements under REACH (Section 1.0.1 of Annex I) and it was not performed in accordance with the OECD TG 443 according to which the study must be adequate for classification and labelling.

It is not possible to conclude on classification and labelling for the Substance due to too low dose level setting, and a hazard characterisation cannot be made. Your dose selection is not appropriate to meet risk assessment and classification and labelling purposes.

Your comments on dose level selection

In your comments you summarise the findings of the OECD TG 408 study including effects, which do not relate to sexual function and fertility, i.e., lower platelet counts, higher cholesterol and phospholipid, and higher kidney weights.

Your key consideration is that "*since this study involved all cohorts, it was considered essential to avoid severe toxicity that might have jeopardized the F1 generation that it is why 200 mg/kg/day which was expected to produce adverse effects on fertility was selected as the high dose level in the EOGRT study.*" Furthermore, you state that "*overall, the Registrants maintain the conclusion that based on all data available at that time, dose levels were selected appropriately with the aim to induce some toxicity, without resulting in unnecessary harm to the animals, and taking into account the objectives of the study, as requested in the OECD TG 443.*"

Specifically, you consider that the lower motor activity (which could negatively affect mating behaviour), decreased prostate weights, decreased number of progressive sperm cells, increased number of stationary sperm cells, and increased number of non-motile sperm would result in impaired male fertility.

ECHA does not agree with your analysis and conclusion.

The original decision unambiguously states that "*The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.*" This request is in line with the ECHA Guidance, which explains that "*the focus of the study in the REACH Annexes is on fertility, which should be considered in the study design of the extended one-generation reproductive toxicity study.*"[7] OECD TG 443 states that if there is "*an insufficient number of pups in a litter to serve all cohorts, the cohort 1 takes precedence […].*" Consistent with OECD TG 443, the original decision also states that the dose-level selection should not result in severe suffering or death.

[7] ECHA Guidance R.7a, R.7.6.2.2.3

ECHA considers that none of the observed effects in the OECD TG 408 study can be considered as severe suffering or death, which could limit the selection of the high dose as such.

Furthermore, it seems unlikely that a lower motor activity in male rats (maximum of -36% at 1000 mg/kg bw/day) could alter mating behaviour to such extend that it would result in a decreased number of pregnancies and offspring. In this respect, you reason that due to the 10-week premating exposure duration, such impairment of mating behaviour could be more likely. However, the effects on motor activity were observed in week 13 of the OECD TG 408 study and therefore after a longer exposure duration compared to the start of the mating in the OECD TG 443. So, there is no support for your claim that the 10-week premating exposure duration could result in even lower motor activity in male rats than that observed in study week 13 of the OECD TG 408.

You also refer to decreased absolute and relative prostate weights. However, it is unlikely that the decreased prostate weights alone result in impaired male fertility. Effects on prostate weights alone are not considered a reliable indicator of reduced male fertility.

Further, you refer to changes of sperm parameters: Decreased number of progressive sperm cells (minimum of 57.4% in high-dose males vs. 71% in control, i.e., a difference of 13.6%), increased stationary sperm cells (maximum of 25.5% in high-dose males vs. 20% in control, i.e., a difference of 5.5%), and increased number of non-motile sperm (maximum of 17.2% in high dose males vs. 9.1% in control, i.e., a difference of 8.1%). It is well-established in scientific literature that "*chemical induced reductions of up to 90% of sperm production can still result in normal fertility rates*"[8] and that "*rats are fertile with 10% of their normal sperm counts, mice with 15-20%. Therefore, in rodents you must get down to a 20-fold reduction of sperm, or about 5% of normal counts, to begin to see an increase in infertility.*"[9] Therefore, the rather slight changes in sperm parameters observed in the OECD TG 408 cannot be expected to result in relevant male fertility problems.

The Wistar Han rat was requested due to the observed changes in sperm parameters and a possible higher sensitivity in this respect. You have met that requirement by performing the EOGRT study with that rat strain. Because the OECD TG 408 study was performed with the Wistar Han strain and the use of this sensitive strain is already reflected in the available results of this study, there is no need to take the "sensitivity of the strain" into account when analysing the results of the OECD TG 408 study.

It is emphasised that no effects on sexual function and fertility were observed in the OECD TG 422 study up to 900 mg/kg bw/day. Although performed in a different rat strain, the screening study does not support your conclusion that there might be a concern for such a severely impaired fertility that the objectives of the EOGRT study would be jeopardised.

Your dose-selection rationale contradicts the requirement defined in the original decision (i.e., that the dose selection should be based on fertility effects) because you reduced the high dose from 1000 mg/kg bw/day in the OECD TG 408 study to only 200 mg/kg bw/day in the EOGRT study to not detect fertility effects, which might jeopardise the production of offspring, although such risk is not indicated based on scientific knowledge of the impact of reduced sperm counts. Your analysis contradicts existing scientific knowledge. According to ECHA Guidance, "*regarding the highest dose level, it is important to ensure that toxicity in both female and male animals is considered to ensure that reproductive toxicity in either gender*

[8] David Jacobson-Kram and Kit A. Keller (editors). *Toxicological Testing Handbook*. CRC Press (Boc Raton, London, New York), 2nd edition (2006), p. 328 of the 2019 paperback edition.
[9] Meistrich, M.L. *Evaluation of Reproductive Toxicity by Testicular Sperm Head Counts*. Journal of the American College of Toxicology; Volume 8(3), 1989, pp. 551-567.

is not overlooked." However, your dose level selection aims at overlooking potential effects on sexual function and fertility in both gender.

As outlined in this decision, a high dose of the limit dose of 1000 mg/kg bw/day should have been selected based on a proper analysis of the existing information to meet the requirement that dose level selection should not cause excessive suffering or death in parental animals and should prioritise the investigation of potential effects fertility.

You also observe a difference between OECD TG 443 and the decision text that dose level selection must be based on fertility effects. You state that "*the main goal of OECD TG 443 is to evaluate the effects on the offspring in addition to parental reproductive effects. Thus, inducing a high level of maternal toxicity such that sexual function and fertility are significantly impaired jeopardizes the main objective of OECD TG 443."*

ECHA agrees that the EOGRT study investigates sexual function and fertility as well as developmental parameters. However, as also the REACH Guidance explains that "*the focus of the study in the REACH Annexes is on fertility, which should be considered in the study design of the extended one-generation reproductive toxicity study. […] Regarding the highest dose level, it is important to ensure that toxicity in both female and male animals is considered to ensure that reproductive toxicity in either gender is not overlooked.*"[10] This is also in line with OECD TG 443 which states that if there is "*an insufficient number of pups in a litter to serve all cohorts, the cohort 1 takes precedence […].*" In other words, investigations on sexual function and fertility take precedence over investigating developmental neurotoxicity and immunotoxicity. Therefore, and as explicitly explained in the original decision, dose level selection must be based on fertility effects.

In your comments you also state that "*based on the available results of DGEBADA, DGEBADA is not a reproductive toxicant. No reproductive/developmental toxicity was noted in the OECD 422 and in the OECD 414 (rat and rabbit) studies up to 900 or 1000 mg/kg/day.*" This statement contradicts your own conclusions on dose level setting, that is the expectation of severe effects on male fertility which could jeopardise the EOGRT study.

ECHA maintains its opinion that there are no indications from any available information that the Substance would cause effects on male fertility even at a limit dose of 1000 mg/kg bw/day that could jeopardise the EOGRT study.

Your comments on animal numbers

You state that because of the high numbers of animals it is not ethically justified to repeat the EOGRT study as it is considered reliable.

ECHA emphasises that it is crucial to design the EOGRT study carefully, also with respect to regulatory requirements, in particular due to the high animal cost. It is the responsibility of the Registrant together with the test laboratory to ensure that the EOGRT study is adequately designed and conducted to meet regulatory requirements.

For the reasons set out above, ECHA maintains its view that the provided EOGRT study is not adequate.

Your comments on dose level selection with respect to the concerns for endocrine activity

[10] ECHA Guidance R.7a, R.7.6.2.2.3

In your comments you explain that although the Substance contains a "*BPA-core […] it is not a structural analogue of BPA*". Furthermore, you state that the existing information shows that the Substance is not a reproductive toxicant and you refer to the following findings in the EOGRT study: Increased mean precoital interval together with a shift to mating at later time points in P0, delayed sexual maturation in F1 (i.e., vaginal opening and achievement of first oestrus and time to first oestrus) with unclear dose response relationship, reduced fertility index at top dose. You explain that all these effects are not treatment related because the changes are either marginal, remain within concurrent or internal control values and/or do not follow a dose-response relationship.

With respect to reduced fertility index, you are correct. There is no effect on this parameter. This has been a mistake in the draft decision. It should have read "reduced mating index" instead of "reduced fertility index" and was corrected.

In your comments, you state that "*It cannot be concluded that the two females that did not show evidence of mating would have mated if the mating period had been extended further and, as stated above, the incidence of non-mating remained within normal ranges.*" In this respect, ECHA clarifies that the situation where animals do not mate within the 14-day mating interval is always considered as a shift beyond the mating interval because animals that do not mate at all, do also not mate within the 14-day mating interval.

In your comments you also refer to historical control data. However, you have not provided any documentation of relevant historical control data. In particular, there is no information about the historical control data provided with respect to number and type of studies, methodologies used, species and strain, number of animals, study years (studies should not be older than 2 years), and statistical parameters of the results (e.g., means, ranges, outliers, standard deviation). Therefore, ECHA is not in the position to evaluate your claims that results are within historical control ranges.

ECHA agrees with your conclusion that from the results of the EOGRT study no conclusions on treatment-relationship and adversity can be made. Based on the analysis described in this decision, ECHA maintains its opinion that these changes indicate a concern for endocrine activity. No conclusions can be drawn due to the too low dose levels (see above).

ECHA disagrees with your conclusion that the Substance is not a structural analogue of Bisphenol A. You explain that the Substance contains the BPA core and does not contain free BPA, but you do not explain why the Substance cannot be regarded as structural analogue of BPA. Because the Substance contains the BPA core flanked by oxygen-containing moieties, ECHA considers that the Substance is a structural analogue of BPA.

ECHA maintains its opinion that the too low dose levels do not address the identified concern for endocrine activity.

Your comments on dose level selection with respect to risk assessment and classification and labelling

You state in your comments that "*based on the study results, the study was considered adequate for the purpose of risk assessment since a LOAEL was derived from the study results based on which a limit value for safe use can be established. Testing a higher dose in a repeat study will not result in a lower NOAEL. For risk assessment purposes, a repeat of the study is therefore redundant, and scientifically not justified, since the OECD 422 and 414 studies were tested near / at limit dose, the data is also sufficient in respect to the CLP criteria.*"

According to your technical IULID dossier, and in contradiction to your comments, you have not observed any adverse effects in the EOGRT study, *i.e.*, no LOAEL was identified, and all NOAEL values for general toxicity, sexual function and fertility, and development were set to > 200 mg/kg bw/day. Therefore, as no LOAEL was identified, and the NOAEL is higher than any of the dose levels tested, it is necessary to repeat the study with adequate dose levels that allows to set a reliable NOAEL and that is a conclusive study for classification and labelling, especially for sexual function and fertility.

With respect to your claim that the data of the OECD TG 422 and 414 studies is sufficient with respect to risk assessment and classification and labelling, ECHA emphasises that the OECD TG 414 study is a pre-natal developmental toxicity study, which does not address the key parameters of the OECD TG 443 study, in particular it does not investigate P0 males, does not expose parental animals before and during mating, does not investigate parturition, lactation and weaning, does not investigate pups and therefore does also not follow up pup development to adulthood, and does not investigate developmental neurotoxicity and developmental immunotoxicity. Also, the OECD TG 422 study does not cover all relevant life stages required by the OECD TG 443, as the extensive postnatal investigations of the fully exposed F1 generation up to adulthood are not included, and it lacks the 10-week premating exposure duration to cover the full cycle of gamete production. Furthermore, the OECD TG 422 study does not investigate developmental neurotoxicity and developmental immunotoxicity, and the statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 pregnant females for each test group as required by the OECD TG 443.

ECHA maintains its view that the EOGRT study is neither adequate for classification and labelling nor risk assessment purposes.

b) Invalid TDAR assay

According to OECD TG 443, performance of the TDAR method should be confirmed as part of the optimisation process by laboratory setting up the assay for the first time, and periodically (e.g. yearly) by all laboratories.

To consider a TDAR method results valid, appropriate results for both negative and positive control groups are needed to show that the results of the dose groups can be trusted.

In this study, a clear indication on the invalidity of the assay is observed due to an increased incidence of non-responders in all groups, *i.e.* the negative control group, three test item groups and the positive control group. In the control group 50% of males and 20% of females where non-responders, where the animals should produce a healthy IgM response following immunisation. In addition, a decrease in the IgM production should be seen in the positive control group, however this cannot be verified due the high number of non-responders in this group as well (70% of males and 40% females).

In addition, it seems that the mean values were calculated for the different test groups considering N=10; *i.e.* non-responders were included in calculating mean values. Non-responders should be excluded from the mean value calculations as they bias the results obtained.

You have also indicated that the incidence of the non-responders was higher than expected and that the decreased response in the cyclophosphamide control group was mild (no historical control data provided).

Taken together, the data generated does not provide reliable basis to assess whether the

Substance has the potential to induced effects in the TDAR assay.

In view of the shortcomings of the TDAR results, you provided a weight of evidence. You explained that no effects on other immune parameters in the EOGRT study were observed to support your view that the findings in the TDAR are negative.

However, and as explained above, the dose-level selection is not adequate because the top dose is too low. Using adequately higher dose levels, effects on other measured parameters relating to the immune system could be observed. Therefore, your weight of evidence approach cannot be accepted.

Taken together, the information on developmental immunotoxicity is not sufficient to conclude on the immunotoxic potency of the Substance in the developing organism because the top dose is too low and the TDAR method is not optimised.

Therefore, you did not meet the request for providing results of the Cohort 3.

Your comments on the invalidity TDAR assay

In your comments you explain why KLH-antigen was used, that inter-animal variability is high with all antigens, that you increased the number to 10 animals per group to improve the statistical power of the analysis, and that mitigation is possible by combining the data of males and females. You also explain that the assay is sufficiently sensitive to detect possible immunosuppressive effects if "*the vehicle control group shows an anti-KLH IgM response*" and the "*positive control group show no anti-KLH IgM response or to a lesser extent when compared to the vehicle control group.*"

With respect to animal numbers, the OECD TG 443 requires that the DIT Cohort contains 10 males and 10 females. Therefore, your argument that you increased the statistical power by increasing the animal number from 8 to 10 animals/sex is not valid.

In your comments, you state that inter-animal variability is known in the TDAR assay and it is not uncommon to see non-responders in the assay.

ECHA agrees with you statement that inter-animal variability is often seen. However, as stated in the Full Study Report (FSR), the incidence of the non-responders was significantly higher than anticipated. It was also stated as follows in the FSR "*Due to the increased incidence of low responses observed, the TDAR assessment may be been less sensitive to detect effects on T-cell dependent antibody responses to KLH*." Due to this, you also considered that TDAR results alone were not sufficient to conclude on the immunotoxicity potential and have therefore developed a weight of evidence approach.

You also consider that due to the high number of non-responders, the results from female and male animals could be combined to improve the statistical power of the assessment.

ECHA agrees that this could improve the statistical power, however by doing so sex dependent effects may be missed. Therefore, combining data from both sexes should not be done, as sexes can have different sensitivities in relation to immune meditated effects.

In your comments, you re-analysed the data by combining the results of males and females and introduced a new threshold indicative of a robust antibody response and summarised the outcome of this analysis in the following table:

Text Table 2
Summary of Animals with a Robust Antibody Response

Group	Males and Females Combined
1 (Control)	6/20
2 (40 mg DGEBADA/kg/day)	7/20
3 (100 mg DGEBADA/kg/day)	8/20
4 (200 mg DGEBADA/kg/day)	9/19
5 (positive control)	0/20

ECHA notes that the number of responders in the negative control is much too low, i.e., only 6 animals (30%) in the negative control showed a robust antibody response whereas 14 (70%) did not. In ECHA's opinion, the numbers should be at least inversed to be considered valid. In general, it can be expected that one or two animals do not respond to the immunisation, however this should not be the case for most of the animals. In this respect, ECHA refers to Gore et al. (2004)[11], which is also referred to in the OECD TG 443, which states that "*immunization of rats with 300 µg KLH by footpad injection resulted in robust antibody response with 100% induction of IgM- and IgG-specific antibodies*" and "*similarly, all rats immunized with KLH (300 µg/kg) by the i.v. route tested positive for anti-KLH IgM and IgG antibodies […].*" Therefore, the negative control group results are not acceptable because adequate KLH-treatment of vehicle-control animals should produce a clear antibody response in most animals. The fact that dose- and negative control groups showed comparable results in your case is not a valid justification for considering that the negative control group is valid. For example, if the negative control group had a majority of responders (as it should be the case), then the analysis of the data would possibly lead to the conclusion that the Substance might exert immunosuppressive properties. Therefore, ECHA agrees with your comment that "*[…] the sensitivity of the actual method developed to evaluate the Immunotoxicity in the Cohort 3 was suboptimal.*"

Independently of the validity of the TDAR assay and the conclusions whether or not the Substance exerts immunosuppressive effects up to the high dose of 200 mg/kg bw/day, and as explained above, the dose levels for the whole EOGRT study including the TDAR assay are inadequately low. A test-item related immunosuppressive effect could occur at higher dose levels and the particular concern for developmental immunotoxicity is therefore not addressed in this EOGRT study.

You also state that "*no pathology findings were detected in the lymphoid organs (i.e., histopathology and organ weight) and no treatment related changes in splenic lymphocyte subpopulations were observed in this study […].*" However, and as already explained in this decision, your weight of evidence is based on the results of this EOGRT study with too low dose levels and test-item related effects on these parameters could be observed at higher dose levels. Therefore, ECHA maintains its view that the weight of evidence does not clarify the particular concern for developmental immunotoxicity for the Substance and is therefore rejected.

ECHA maintains its opinion on the invalidity of the TDAR assay and that the too low dose levels do not address the identified concern for development immunotoxicity.

c) Your comments on the requirement of an EOGRT study under Annex IX

[11] Gore, E.R., J. Gower, E. Kurali, J.L. Sui, J. Bynum, D. Ennulat and D.J. Herzyk (2004), "Primary Antibody Response to Keyhole Limpet Hemocyanin in Rat as a Model for Immunotoxicity Evaluation", Toxicology, 197, 23-35.

In your comments you request that "*based on the adverse effects on male fertility including the lower prostate weight identified in the 90-day repeated toxicity study, the Extended one-generation reproductive toxicity study (OECD TG 443) should be requested at the Annex IX of REACH and not only at the Annex X.*"

This request contradicts your conclusion that "*based on the available results of DGEBADA, DGEBADA is not a reproductive toxicant. No reproductive/developmental toxicity was noted in the OECD 422 and in the OECD 414 (rat and rabbit) studies up to 900 or 1000 mg/kg/day. This was confirmed by the current EOGRT study […].*"

ECHA does not consider that the observed findings in prostate weight and sperm parameters in the OECD TG 408 without functional impairment (see OECD TG 422) meets the condition for making the EOGRT study a requirement under Annex IX to REACH (adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity).

d) Conclusion

As explained above, the dose-level selection to detect reproductive toxicants and developmental immunotoxicants is inadequate. Furthermore, the TDAR is considered invalid and there is a concern for endocrine activity that is not clarified due to inadequate dose-level selection.

Therefore, the request in the original decision is not met, and you are still required to provide an Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in Wistar rats, oral route with the registered substance specified as follows:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

As explained above, a top dose of 1000 mg/kg bw/day seems adequate.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[12].

B. Test material

ECHA notes that in the dossier, under the test material information, there is a reference to the substance '[redacted]'. However, this is inconsistent with the identifiers of the registered substance as defined in section 1.1 of the IUCLID dossier, which unambiguously refer to the oligomer substance with EC number 500-130-2. The registered substance is the result of the [redacted] providing several [redacted] (e.g. [redacted]) and not only '[redacted]'. Therefore, the test material must represent the registered substance as identified in section 1.1 of the IUCLID dossier. In addition, it is important that you report the exact concentrations of the identified constituents for the test material.

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier

a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as

[12] https://echa.europa.eu/practical-guides

their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[13].

[13] https://echa.europa.eu/manuals

Appendix C: Procedure

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 24 October 2017 ("the original decision"). Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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 adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[14] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[15]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[16]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[17]

[14] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[15] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[16] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[17] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.