~~Confidential~~

Helsinki, 05 January 2024

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
07 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(s):

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 in the original decision.

Reasons for the request(s) are explained in the following appendix entitled "Reasons to request information required under Annex 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 (2020) 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:

a) Dose level selection

The original decision requested that the dose level setting shall aim to induce some toxicity at the highest dose level 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.

Similarly, according to paragraph 21 of the OECD TG 443, the highest dose should be chosen with the aim to induce some systemic toxicity, but not death or severe suffering of the animals. Paragraph 22 of the OECD TG 443 also states that, "*in the dose selection the investigator should also consider and ensure that data generated is adequate to fulfil the regulatory requirements across OECD countries as appropriate (e.g., hazard and risk assessment, classification and labelling, ED assessment, etc.).*" In this case, the objective is to investigate reproductive toxicity (Column 1, Section 8.7, Annex X of REACH), in particular fertility, for the purpose of both classification and labelling, and risk assessment (e.g., recital 7 of Regulation 2015/282). The dose selection is thus to be based upon the fertility effects.

You provided an EOGRT study (2020) with a highest dose of 200 mg/kg bw/day (*i.e.* 20% of the limit dose) and showing various effects. On that basis, you derived a NOEL (no observed effect level) and a LOEL (lowest observed effect level) but no NOAEL (no observed adverse effect level) or LOAEL (lowest observed adverse effect level).

You explain that the highest-dose selection for the OECD TG 443 study was based on "*the results of previously conducted (repeated and reproduction) toxicity studies with oral exposure of DGEBADA in rats*". 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.*"

Your dossier provides the following which is relevant for assessing your selection of the highest dose for the OECD TG 443 study:

- The OECD TG 422 study used dose levels of 0, 100, 300 and 900 mg/kg bw/day. This study established a NOAEL of >900 mg/kg bw/day for parental and reproductive/developmental effects, in absence of adverse effects at the highest dose.

This study showed that there are no effects on systemic toxicity and sexual function and fertility.

- The OECD TG 414 study used dose levels of 100, 300 and 1000 mg/kg bw/day. It established a NOAEL of >1000 mg/kg bw/day for maternal and developmental toxicity, in absence of adverse effects at the highest dose. This study showed absence of effects on systemic toxicity and on maintenance of pregnancy.

- The OECD TG 408 used dose levels of 100, 300 and 1000 mg/kg bw/day. It established a NOAEL of <100 mg/kg bw/day for systemic toxicity. It showed the following effects:
    a. Locomotor activity was statistically significantly reduced over all measured time points in males only at the highest dose of 1000 mg/kg bw/day (643 vs 997 total low beam counts) and after 30 minutes at the mid dose of 300 mg/kg bw/day and highest dose of 1000 mg/kg bw/day (28 and 22 total beam counts vs 74) during week 13 of exposure.
    b. Changes in some biochemistry parameters were observed in a dose-dependent manner after 13 weeks of exposure. These included decreased glucose in mid and high-dose males (not observed in females), cholesterol in all male dose groups and in mid and high-dose females, phospholipids in all male dose groups and mid and high-dose females, decreased potassium in mid and high-dose males (not observed in females), decreased protein in high-dose males (not observed in females) and decreased globulin in high-dose males (not observed in females).
    c. Progressive sperm showed an absolute decrease of 7.6% in mid-dose males (300 mg/kg bw/day). Accordingly, stationary and not motile sperm showed an absolute increase of 4.3% and 3.3%.
    d. Statistically significantly decreased absolute and relative prostate/seminal vesicles weights were observed from the mid-dose group without histopathological correlates in the OECD TG 408 study after 13 weeks of exposure.

ECHA notes, first, that the EOGRT study was not using a limit dose and did not show adverse effects, as you indicated by identifying only a NOEL and a LOEL. It is, therefore, essential to ensure that the highest dose fulfilled the related requirements of REACH and OECD TG 443 identified above to ensure that the EOGRT study is designed to investigate reproductive toxicity.

Second, in your registration dossier, you claim to have taken into account the results of all repeated and reproductive toxicity studies when setting the top dose in the EOGRT study. Your reasoning itself, however, refers exclusively to the OECD TG 408 study and it is then unclear how you have weighted the results of all repeated and reproductive toxicity studies.
In your comments to the draft decision, you indicate that you gave full weight to the results of the OECD TG 408 study in Wistar rats, which showed some effects, and no weight to the reproductive toxicity studies in Sprague-Dawley rats because these showed no relevant effects up to the highest dose. You also state that the highest-dose selection for the OECD TG 443 study was based on fertility effects (sperm motility and prostate weight) and the facts that effects were seen at all doses tested in the OECD TG 408 and you considered that the Wistar rat is the most sensitive strain.

Although the Wistar rat might be more sensitive as also stated in the original decision, the available information does not clarify if that is the case, in particular due to the lack of studies of comparable exposure duration.

This weighting does not appear to be based on objective scientific criteria considering that:

a) there is no toxicity, i.e., no *adverse* effects, observed below 300 mg/kg bw day in the OECD TG 408. In particular:
    a. Change in one sperm parameter: In analogy and applying a worst-case assumption (considering that the sperm with reduced motility is not available for fertilisation), 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*" 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.*" OECD GD recommends a minimum value of 70% motility for control animals to produce a valid negative control with a safety margin not to produce fertility effects such a lower conception rates. In the OECD TG 408 study, the low- and mid- dose groups are close to the recommended value for negative control groups with 64.5% and 63.4%, respectively. Such reduction is unlikely to result in decreased conception rates, for example.
    b. Decrease in prostate/seminal vesicles weights: a *statistical significant* decrease was observed from mid-dose (300 mg/kg bw/day) and after longer relevant exposure duration than for an EOGRTS and in absence of histopathological correlates, indicating that a top dose higher than 200 mg/kg bw/day may be warranted.
b) the relevant exposure duration for functional fertility is shorter in the EOGRT study compared to that of the OECD TG 408 study, because the majority of animals are exposed 10-11 weeks until successful mating in the EOGRT study, while the exposure duration in the OECD TG 408 is 13 weeks, resulting in the possibility to miss effects on other fertility parameters such as conception rate. In this respect, you highlight that exposure duration of males is similar between the EOGRT study and the OECD TG 408 study, but you did not consider the fact that animals are mated after study week 10, i.e. a critical event for the assessment of reproductive toxicity, while measurements are done in week 13 in the OECD TG 408 study; on that basis, it is not known whether the prostate effects observed in the OECD TG 408 study would be already present at study week 10. Furthermore, the OECD TG 422 and 414 are more relevant for designing the EOGRT study because they address exposure during sensitive periods such as mating, gestation, parturition, and foetal/neonatal/pup development;
c) although the effects on sperm motality and prostate/seminal vesicle weight were only observed in the OECD TG 408 study in Wistar rats, the absence of dose-limiting effects in both the Wistar and the Sprague-Dawley rats should have been considered for dose-level selection. The available studies do not clarify whether there are different sensitivities in the two different rat species with respect to systemic toxicity, severe suffering and death; and
d) the reproductive toxicity studies are reliable and provide relevant information on both systemic and reproductive toxicity for setting the top dose in the EOGRT study.

For completeness, ECHA also notes the following on the other, non-fertility, effects observed in the OECD TG 408 study:

    a. Locomotor activity: *statistically significant* activity was only observed in males at the highest dose of 1000 mg/kg bw/day for all time points and at 30 minutes from the mid-dose of 300 mg/kg bw/day, but also during study week 13 of exposure, which is beyond the exposure duration for mating of an OECD TG 443 study for parental animals. This decision is consistent with original decision because it also clarifies that the changed locomotor activity is a high-dose concern.

b. Changes in some biochemistry parameters: (i) biochemistry parameters are inherently variable due to significant background variation, (ii) the observed changes are rather small/moderate, (iii) some changes occurred only in males but not in females, (iv) some changes reached statistical significance only at mid and/or high-dose levels, and (v) some tissue (e.g. liver) correlates in a few/ individual animals at 1000 mg/kg bw/day.

For all these reasons, you have not demonstrated that the top dose in the EOGRT study was aiming to induce some toxicity at the highest dose level to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. As a consequence, the EOGRT study (2020) must be rejected.

b) Unreliable immunotoxicity assay (TDAR assay)

The original decision requested the developmental immunotoxicity cohort 3 which, under OECD TG 443, requires the TDAR assay. Such assay must be conducted using an appropriate antigen for immunisation and either PFC response or the ELISA method (OECD TG 443, para. 52). For the results of such assay using the ELISA method to be considered reliable the following applies:

- the antigen used results in a preferably quantitative, robust antibody response in terms of increased IgM at least in the negative control group. This is based on Gore et al. (2004)[3], which is also referred to in the OECD TG 443, "*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 […].*" Such robust antibody response is to show that the immunisation with the antigen has succeeded;

- a decrease in the IgM production is seen in the positive control group.

In the EOGRTS provided by you IgM was used as antigen and the ELISA method was applied. In the results of this study, first, an increased incidence of non-responders was observed 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.

Second, 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 in the registration dossier). In the Full Study Report on page 67, it is stated *"Due to the increased incidence of low responses observed, the TDAR assessment may have been less sensitive to detect effects on T-cell dependent antibody responses to KLH.".* To support the claim in your comments, that it is not uncommon to encounter non-responders, you have provided historical control data indicating ranges of IgM antibody values.

ECHA notes that the historical control data values only provides information on the ranges of IgM values. However, it does not provide information of non-responders seen in those 40 animals reported, i.e. how many non-responders were in a study from which the historical control data was collected. Moreover, it is not clear whether the historical control data provided in the comments refers to the test house historical control data where the EOGRT

[3] 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.

study was performed or to the historical control data of the test site where the anti-KLH IgM samples were shipped for re-evaluation due to the invalidity of the results obtained by the original test house. This is important, as a different validated ELISA method was used in the other test facility.

ECHA agrees with the issues that you have identified in the results of the control groups and test items groups. The significant percentage of non-responders in the concurrent (negative) control group, especially in male animals where only 50% showed a response following immunization with the antigen. This indicates performance related issues in the antigen used, as it did not lead to robust antigen response. This antigen was used in all test item and control groups but the corresponding results cannot be interpreted as it is possible that that the antigen was actually not effective in immunization, as indicated above. Therefore, it is not possible to conclude on any of the results.

As non-responders were seen in all of the test groups, including the positive control group, no conclusion can be made whether the results obtained from the positive control group are showing relevant degree of immunosuppression from a known immunosuppressant, as indicated in the comments, or whether the results are linked to the KLH antigen used in this test and its inability to produce robust antibody response.

You identified the issues of the TDAR results, but you argued that these issues are remedied based on a weight of evidence approach. You explained that no effects on other immune parameters in the EOGRT study were observed to support your conclusion that the findings in the TDAR are negative.

However, a weight of evidence approach based on the various results of the EOGRT study cannot remedy these issues. 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.

For these reasons, the TDAR assay is unreliable.

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

c) Conclusion

As explained above, the dose-level selection is inadequate and the results of the TDAR are unreliable.

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).

A highest dose of 1000 mg/kg bw/day (i.e. the limit dose) 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[4].

B. 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:

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- 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

- 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.
- 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 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 (https://echa.europa.eu/manuals).

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

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 C: List of references - ECHA Guidance[5] 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)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

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[8]

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[8] 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 D: 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.