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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For 2,5-di-tert-pentylhydroquinone (DAHQ), CAS No 79-74-3 (EC No 201-222-2)

Addresses:Registrants of 2,5-di-tert-pentylhydroquinone (Registrant(s)) [1]

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent for comment, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrants holding active registrations on the day the draft decision was sent are *not* addressees of this decision if they are: i) Registrant(s) who had on that day registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by the Health & Safety Executive as the Competent Authority of the United Kingdom (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 6 May 2015 i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of the United Kingdom has initiated substance evaluation for 2,5-di-tert-pentylhydroquinone (DAHQ), CAS No 79-74-3 (EC No 201-222-2) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Environment/Suspected PBT; Exposure/High RCR, 2,5-di-tert-pentylhydroquinone was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of the United Kingdom was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding skin sensitisation potential, DNEL derivation and human health exposure.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 24 March 2015.

On 6 May 2015 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 12 June 2015 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

The evaluating MSCA considered the comments received from the Registrant(s) and the additional information provided in July 2015.

On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 3 September 2015 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, two Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 10 October 2015 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

Referral to the Member State Committee

On 19 October 2015 ECHA referred the draft decision to the Member State Committee.

By 9 November 2015, the Registrant(s) provided comments on the proposals for amendment, in accordance with Article 51(5). In addition, the Registrant(s) provided comments on the draft decision. The Member State Committee took the comments on the

proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant(s)' comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 7 to 11 December, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 7 December 2015.

ECHA took the decision pursuant to Article 52(2) and Article 51(6) of the REACH Regulation.

II. Information required

In reply to proposals for amendment and the Registrant(s)' comments on them, it is clarified that given the complexicity of the concerns identified for the substance, it is currently difficult to identify what follow-up, including which further risk management measures, will be necessary.

To address the PBT concerns:

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods/instructions (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. Water solubility (OECD 105)
2. Partition Coefficient (1-Octanol/Water): Slow-Stirring Method (OECD 123)
3. 21-day *Daphnia* reproduction toxicity study (OECD 211)
4. Fish Early Life Stage test (OECD 210). The need for this test is dependent on the results for tests 3, 6 and 7 as further specified in section III below.
5. Freshwater Alga and Cyanobacteria, Growth Inhibition Test (OECD 201)
6. Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test (OECD 309)

   The need for this test depends on the outcome of test 2 as further specified in section III below. The simulation test shall be performed at a temperature of 12°C, and include the identification of transformation products.
7. Bioaccumulation in fish: Aqueous and Dietary Exposure test (OECD 305)

   The need for this test depends on the outcome of test 2 and 6 as further specified in section III below.

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information regarding the registered substance subject to the present decision:

8. PBT assessment of all relevant impurities present in the registered substance at levels of 0.1% w/w or more.

To address the environmental exposure concerns:

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods (in accordance with Article 13 (3)

and (4) of the REACH Regulation) and the registered substance subject to the present decision:

9. Adsorption – desorption using a batch equilibrium method (OECD 106)

   The need for this test depends on the outcome of test 2 as further specified in section III below.

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information regarding the registered substance subject to the present decision:

10. Provide monitoring of DAHQ in effluent being discharged to municipal sewer at production site.

To address the additional concerns:

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test method (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

11. Skin sensitisation: Local Lymph node Assay (OECD 429)

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information regarding the registered substance subject to the present decision:

12. Information on the DNEL derivation as follows:

a) Relevant historical control rates for thyroid effects observed in the 90-day rat study;
b) Any available evidence to support the Mode of Action for induction of thyroid toxicity and human health relevance;
c) revision of the DNEL derivation using the ECHA guidance (ECHA Guidance on Information Requirements and Chemical Safety Assessment, chapter R.8)

13. Information on suitable glove materials, thicknesses and breakthrough times

Further information on worker exposure, more specifically information on the operating conditions that are anticipated where DAHQ is used and an indication of whether the parameters that have been used to model exposures are based on assumptions or information communicated by downstream users.

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **1 March 2020** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report. However, if the requested biodegradation simulation test (OECD 309) (requirement 6 above) is not needed, the deadline for the registration(s) update shall be **30 August 2018**.

The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

A. PBT concerns

DAHQ is not readily biodegradable and therefore screens as P and vP. The substance has a measured octanol-water partition coefficient value (log Kow) of 3.3. However, this is in contrast to predicted log Kow values of between 4.38 - >7.08. The measured water solubility (<0.08 mg/l) and measured log Koc (3.68) are also more likely to be associated with a substance with a log Kow value higher than 3.3. Due to the uncertainty, ECHA considers that the substance screens as B and vB on the basis of QSAR predictions. The current acute aquatic ecotoxicity L(E)C50 values for the chemical are all at, or below 0.1 mg/l, which is the screening threshold for T(ecotoxicity).

Overall, based on present information, ECHA considers that the substance screens as both PBT and vPvB. The information requested under points 1- 8 are required in order to address the PBT concerns.

1. Water solubility

The current measured water solubility data are insufficient to allow interpretation of the ecotoxicity studies. This is because the analytical detection limit results in an unbounded water solubility value of <0.08 mg/l. The Registrant(s) are required to perform a repeat test using a more accurate analytical method. This is important to ensure that the repeat ecotoxicity studies required and, if triggered, the bioaccumulation study in this assessment can be conducted using concentrations below the water solubility limit. The analytical development required for this study will also be useful for those tests. An accurate water solubility value is also important for the environmental risk assessment to ensure that appropriate PECs are derived.

The Registrant(s) questioned whether a more accurate value can be derived. However their principle argument is that the analytical detection limit was developed based on an expectation of a higher water solubility value. In the opinion of ECHA, this does not show that a lower water solubility cannot be measured, merely that the analytical method chosen was expected to be fit for purpose, but wasn't.

The Registrant(s) also cited possible absorption to the container, and the potential variable analytical results at low concentrations, as confounding the measurement. These issues for obtaining a quantified water solubility value below the current "open-ended" one are possible, but if these do occur it is unclear whether they would significantly interfere with the measurement. For example it is possible that such interference occurs at concentrations below the true water solubility value.

In any case, the arguments would also suggest that reliable measurement of water solubility is generally not possible below 0.08 mg/l. ECHA is not convinced by this argument as the REACH endpoint guidance 7A indicates sensitivity of the test guideline to be 1 µg/l (appreciating this is not an analytically derived value). There are also examples of highly absorptive substances with measured water solubilities below 0.08 mg/l, for example a number of highly hydrophobic halogenated flame retardants.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Water solubility (OECD 105).

2. Partition Coefficient

The octanol-water partition coefficient of DAHQ was measured in a GLP study according to OECD 117, HPLC method and a log Kow of 3.3 was determined. Whilst the study was considered reliable (Klimisch score of 1) the test report stated that the predicted log Kow was 6.2 (Rekker method) which is outside the range of the HPLC method (log Kow 0-6).

Due to the significant difference between the predicted and measured data, the partition coefficient of DAHQ was further considered and using different calculation methods the following values were predicted:

Values of the octanol-water partition coefficient for DAHQ

Method	Log Kow value
OECD 117	3.3
Back calculation from measured Koc (3.68) using KOCWIN v2.00	4.38
KOWWIN (v1.68)	5.83
Rekker	6.2
Back calculation from water solubility (<0.08 mg/l) using WSKOW v1.42	>7.08

Given this weight of evidence suggesting that the log Kow might be higher than currently measured, there is sufficient uncertainty to require more information for this endpoint. The log Kow value is important for bioaccumulation screening and input to QSARs for ecotoxicity and bioaccumulation. The repeat test should be performed using the slow stirring method, which is recommended for substances with an expected log Kow >5 and is considered the most appropriate and accurate method for highly hydrophobic substances such as DAHQ.

The Registrant(s) commented that they do not agree a new log Kow study is needed, citing the available value from a modern OECD 117 test. ECHA's concern is that when considered together, the water solubility and partition coefficient values appear contradictory: for a chemical with a measured solubility below 0.08 mg/l one would generally expect it to have a log Kow value above 3.3. It is appreciated that there may be exceptions to this assumption, however in this case there are two further lines of evidence supporting the concern:

- The estimations of log Kow from different QSARs for DAHQ derived by ECHA all exceed the measured value by between one and four orders of magnitude. In particular, the predicted value of 5.83 from a recognised QSAR (KOWWIN) exceeds the threshold for B/vB screening.

- The registrant has expressed concern that significant adsorption might occur in the repeat water solubility test confounding the measurement. In the view of ECHA, this type of significant adsorption would generally be expected for a substance with log Kow well above 3.3.

The new dissociation constant data has addressed one possible reason for the disparity between water solubility and log Kow. However this is not sufficient to validate the log Kow value of 3.3. One further possibility considered by ECHA is that the substance is insoluble in all solvents. However technical data on the manufacturers website does not indicate that this is the case (for example solubility in ethanol and methanol are indicated to be 68 and >100 g/100g solvent at 25 °C respectively).

Overall the weight of evidence suggests that the substance may well have a log Kow value higher than 3.3. Therefore, ECHA considers that there are sufficient grounds to doubt the value derived from the available physico-chemical testing, and require a further study to be

performed.

The Registrant(s) have also raised some practical concerns for the slow stirring method. These are that the method is designed for substances with log Kow >5, which they do not believe to be the case for DAHQ, i.e. that it is difficult to prevent adsorption in the aqueous phase which confounds the results; and that analytical variablity may result in an invalid study. ECHA agrees that the test is principally aimed at more hydrophobic substances. However, the study is valid for all ranges of log Kow. Therefore, regardless of the actual log Kow value of DAHQ, the OECD 123 method is expected to be suitable for performing the measurement. Since the test guideline is specifically aimed at hydrophobic chemicals, in the opinion of ECHA, the potential difficulties highlighted by the registrant are no different to those experienced with other adsorptive chemicals. Concerns with the current analytical method were highlighted by ECHA as the principal reason for repeating the water solubility study. Therefore such a method would then be available for the new log Kow test. Contrary to the Registrant(s)'s comment, none of the QSARs used by ECHA determine a log Kow <4.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Partition Coefficient (1-Octanol/Water): Slow-Stirring Method (OECD 123).

3. Chronic Daphnia study

The acute / chronic aquatic invertebrate endpoint is needed for both assessing T for PBT and in the derivation of the aquatic PNEC for the environmental risk assessment.

There are no valid acute invertebrate data for the substance. The available data are confounded by being performed above the water solubility limit of the chemical without analytical support. This means it is not possible to determine whether physical effects caused the apparent toxicity or the amount of substance that was in solution.

As the substance has a low water solubility value, it is considered more appropriate to conduct a chronic *Daphnia* test. While a repeat acute *Daphnia* test could be performed, if there are no effects in that study, a chronic test would still be required to provide an aquatic PNEC. An alternative would be to try to replicate the solution preparation of the previous acute *Daphnia* toxicity study, and determine analytically the dissolved concentration. However, in this case, it is not considered practical and reliable due to the age of the original test. Additionally, if that assessment determined no effects occurred below the water solubility of the substance, it is likely that the chronic study would still be required.

In their comments the Registrant(s) agreed to the testing however they proposed to utilise a "saturated solution method". ECHA are not clear what the Registrant(s) mean by this and suggests they should consult the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD Series on Testing and Assessment Number 23)for advice on testing low solubility chemicals prior to performing the test.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: 21-day Daphnia reproduction toxicity study (OECD 211).

4. Fish Early Life Stage toxicity test (FELS)

The acute / chronic fish endpoint is needed for both assessing T for PBT and in the derivation of the aquatic PNEC for the environmental risk assessment.

There is uncertainty in the acute fish toxicity dataset for the substance because the available data are confounded by being performed above the water solubility limit of the

chemical without analytical support. This means it is not possible to determine whether physical effects caused the apparent toxicity or the amount of substance that was in solution. However it is noted that a number of results, based on nominal values, consistently suggest toxicity around 13-67 µg/l. As the substance has a low water solubility value, it is considered to be more appropriate to conduct a chronic fish test to address this uncertainty. While a repeat acute fish test could be performed, if there are no effects in that study, a chronic test would still be required to provide an aquatic PNEC.

An alternative would be to try to replicate the solution preparation of the previous acute fish toxicity studies, and determine analytically the dissolved concentration. However, in this case, it is not considered practical and reliable due to the age of the original tests. Additionally, if that assessment determined no effects occurred below the water solubility of the substance, it is likely that the chronic study would still be required.

In the interests of animal welfare the chronic *Daphnia* test (requirement 4) should be performed before the FELS test. If the chronic *Daphnia* test determines a NOEC < 0.01 mg/l (i.e. indicating that DAHQ meets the T criterion), the FELS test would not be necessary unless the substance was not found to be PBT, in which case it would still be required for the PNEC assessment. If however the *Daphnia* NOEC is above 0.01 mg/l, the FELS test is then required to address the uncertainty in the aquatic PNEC. This is because the acute data tentatively suggests that fish could be more sensitive than *Daphnia*. The measured fish acute toxicity (96-h LC50) is around 0.013-0.067 mg/l compared to a measured acute *Daphnia* toxicity (48-h EC50) of 0.91 mg/l (with no effects observed at 0.32 mg/l). This sensitivity assessment is limited by the questionable reliability of the available test data.

While a repeat acute fish test (or a Fish Embryo Toxicity study) could be performed, it is unlikely that this would negate the need for a chronic test. If there are no effects in the study, a chronic test would still be required to provide an aquatic PNEC. This is because from the acute information, fish appear more sensitive than *Daphnia*. If there were effects in a repeat acute test, this would confirm the available acute fish effects and trigger chronic testing to address T for PBT (unless, as above, the new long-term *Daphnia* test already indicated "T").

In their comments the Registrant(s) agreed to the testing (dependent on the result of the chronic *Daphnia* study); however, they proposed to utilise a "saturated solution method". ECHA are not clear what the Registrant(s) means by this and suggests they should consult the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD Series on Testing and Assessment Number 23)for advice on testing low solubility chemicals prior to performing the test.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Fish Early Life Stage toxicity test (OECD 210).

5. Algal Growth Inhibition Test

There are no valid algal toxicity data for the substance. The available data are confounded by being performed above the water solubility limit of the chemical without analytical support. This means it is not possible to determine whether physical effects caused the apparent toxicity or the amount of substance that was in solution.

An alternative would be to try to replicate the solution preparation of the previous algal inhibition study, and determine analytically the dissolved concentration. However, in this case, it is not considered to be practical and reliable due to the age of the original test. The algal and aquatic plants toxicity endpoint is needed for both assessing T for PBT and in the derivation of the aquatic PNEC for the environmental risk assessment.

In their comments the Registrant(s) agreed to the testing; however, they proposed to utilise a "saturated solution method". ECHA are not clear what the registrant means by this and suggests they should consult the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD Series on Testing and Assessment Number 23)for advice on testing low solubility chemicals prior to performing the test.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision:
Freshwater Alga and Cyanobacteria, Growth Inhibition Test (OECD 201)

6. Simulation Biodegradation Test

The need for this test depends on the result of the requested partition coefficient study (request 2).

DAHQ is not readily biodegradable and screens as P/vP. If the substance also screened as B/vB an environmental simulation biodegradation study would be required to determine if the substance meets the P or vP criteria in Annex XIII of REACH. The current log Kow data are uncertain and so it is unclear whether the substance screens as B/vB. Therefore the requirement for a simulation test is only required if the new log Kow measurement determines the partition coefficient of the chemical to ≥4.5. This value would indicate that DAHQ screens as B/vB, and would therefore potentially be vPvB and PBT. If the log Kow is confirmed to be less than 4.5, the substance does not screen as PBT or vPvB, and the simulation biodegradation test is not required.

The OECD 309 should be performed if technically possible as this excludes the likelihood of bound residues being formed which can confound interpretation of the OECD 307 or 308 study.

The Registrant(s) argue that this test is not necessary as the log Kow indicates the substance does not screen as B/vB. As stated above, ECHA is not satisfied that the available weight of evidence for log Kow demonstrates with confidence that the chemical can be excluded as screening as B/vB.

In their comments the Registrant(s) suggest that the reliability of log Kow diminishes above 6. It is not fully clear to ECHA the relevance of this comment to DAHQ (where the Registrant(s) claim a log Kow of 3.3); however, ECHA disagrees with the context of the comment that no substantial bioconcentration is assumed for compounds for log Kow greater than 6. ECHA agrees that it is generally accepted that BCF values from an aqueous fish bioconcentration test may decrease with increasing log Kow above 6, for instance the REACH R11 PBT guidance (p55) states that at log Kow >6 "a decreasing relationship between [log Kow and BCF] is seen". However this does not mean a log Kow > 6 can safely be used to exclude a substance from PBT assessment (i.e. as not B/vB). ECHA highlights that bioaccumulation exclusion criteria includes a (calculated) log Kow value >10 which is significantly higher than 6. There are a number of examples of chemicals with log Kow >6, which have been determined as being either B or vB based on bioaccumulation data.

In the opinion of ECHA a decision on whether DAHQ screens as B/vB or not cannot be made with confidence until a new log Kow study has been performed.

In the original draft decision, a choice between OECD 308 and OECD 309 was given. However, a Member State proposed that only the OECD 309 study should be performed, as in their opinion this test is sufficiently suitable to determine the biodegradation of DAHQ. They considered that based on a QSAR prediction (EPIWIN) of 930 µg/L (US-EPA 2012) and the current measured value (<80 µg/l), new measured data to confirm that the substance

would be within the applicability domain of the OECD 309 test guideline (>10 µg/l) are necessary.

ECHA agrees that the benefit of the OECD 309 method is that it excludes the likelihood of bound residues being formed which can confound interpretation of the 308 study. However, in addressing the proposal for amendment, ECHA notes that the feasibility of OECD 309 is broader than just water solubility, for example adsorption and analytical ability may also be important. ECHA also considers there is uncertainty in the water solubility prediction as this over-estimates the current measured water solubility value by more than an order of magnitude, so this may not be a good guide for the true water solubility. On this basis the Decision has been revised to only require OECD 309 in section II, but if technical infeasibility is shown by the Registrant(s), submission of an Aerobic and Anaerobic Transformation test in Aquatic Sediment Systems OECD 308 at 12°C is permitted instead. In this circumstance the Registrant(s) shall provide justification for why the OECD 309 test was not feasible.

A second proposal for amendment proposed to perform the simulation testing at 12 °C to represent the average environmental temperature for the EU. ECHA agrees with this, and the Decision was updated accordingly.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision, if the new log Kow measurement determines the partition coefficient of the registered substance to be ≥4.5:
Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test (OECD 309). The test needs to be performed at a temperature of 12 °C to represent the average environmental temperature for the EU and include the identification of the degradation products.

7. Bioaccumulation in fish

The need for this test depends on the result of the requested partition coefficient study (request 2) and simulation biodegradation test (request 6).

The Registrant(s) has provided a series of QSARs and category approach to fulfil the bioaccumulation information requirement in the registration dossier. ECHA considers that these do not meet the requirements of Annex XI of REACH and are insufficient to fulfil the endpoint.

In the registration dossier, the Registrant(s) predict a fish bioconcentration factor (BCF) of 41.91 L/kg (wet weight, ww) using the BCFBAF v3.00 model and a log Kow input value of 3.3. As noted above under section III.A.2, ECHA considers that the log Kow value is uncertain, which makes BCF values predicted from log Kow also uncertain. ECHA notes that if a log Kow of 5.83 is used in the same model, this suggests the BCF value is close to 2000.

The Registrant(s) have also provided QSAR predictions using three other models: BCF model (CAESAR) version 2.1.11, BCF Read-across (v1.0.0) and T.E.S.T. (v4.1). The Registrant(s)' QPRF for CAESAR states that the applicability domain of CAESAR for DAHQ is borderline because "similar molecules in the training set have experimental values that strongly disagree with target compound predicted value". ECHA has significant concerns that all but one of the analogues used in the CAESAR prediction had measured BCF values that were under-predicted by CAESAR. Two (2,6-di-tert-butyl-4-ethylphenol and tri-tert-butylphenol) were *predicted to have log BCF values significantly below 3.3* [i.e. BCF =

2000]*, whereas the true value is much higher* (Zhao et al 2008[3]). This suggests the model could under-predict the BCF value for DAHQ (predicted to be 44). The value predicted for DAHQ also appears to be an outlier compared to the measured values for the six analogues.

The BCF read-across v1.0.0 model uses the same six analogue chemicals as CAESAR, but in contrast predicts the BCF of DAHQ to be 1268.

The output for the TEST model provides BCF results (251 – 3467) for five analogue chemicals chosen by a molecular descriptor approach. The results are combined to give an overall BCF result of 667 for DAHQ. A QMRF is not available for the TEST model, and ECHA considers the similarity of some of the analogues to DAHQ to be low (for example bisphenol-A and fenpropidin). The other three analogues are present in the CAESAR dataset. TEST predicts the BCF of DAHQ to be 667.

Overall the read-across QSAR models predict the BCF of DAHQ to be between 44 and 1285. In at least one case the model under-predicts the analogues, and for another, some of the analogues are questionable. A major concern of ECHA is that none of the QSARs appear to contain measured data for a hydroquinone. This means it is uncertain whether QSARs based on other structures are able to accurately predict the bioaccumulation of the hydroquinone functional group, and therefore of DAHQ.

The QSAR models based on log Kow predict the BCF of DAHQ to range between 41 and 1969. These depend on the measured log Kow value, and again a significant concern is that the model datasets do not appear to contain measured data for a hydroquinone. This means it is uncertain whether QSARs based on other structures are able to accurately predict the bioaccumulation of the hydroquinone functional group, and therefore of DAHQ.

The Registrant(s) take a geometric mean of the four QSAR values to provide an overall BCF of 199. They justify this based on the approach for ecotoxicity data described in REACH guidance R10 (characterisation of dose-response for the environment). However, this guidance does not mention QSAR data, and is specific to measured data where there are several studies of the same species/endpoint. Putting this concern aside, the Registrant(s) also include the caveat provided in the guidance that the geometric mean can be applied "if results are not more than one order of magnitude apart". The QSAR bioaccumulation predictions provided by the Registrant(s) have a range between 41.91 and 1268, and so is considerably in excess of one order of magnitude. Taking the geometric mean is therefore inappropriate for the bioaccumulation data. In principle the highest reliable value should be selected instead.

Overall ECHA does not consider the QSAR predictions to meet the requirements of Annex XI. The outputs are not assessed to be reliable, principally as the models do not provide an adequate weight of evidence due to the inconsistent values, and do not appear to contain any measured data for chemicals containing the hydroquinone functionality.

Paragraph 1.5 of Annex XI of REACH lists the different forms of similarity that may be used to build a category. However, the basis for the category approach provided in the registration dossier has not been explained or justified by the Registrant(s), for example based on structure or physicochemical data. This means its validity and applicability to DAHQ is unclear as the similarity is not adequately demonstrated. It is also unclear where DAHQ would fit into the category as this is dependent on the log Kow value, which is currently considered by ECHA to be uncertain.

A major concern of ECHA is the lack of valid, measured bioaccumulation data for any

[3] C. Zhao, E. Boriani, A. Chana, A. Roncaglioni, E. Benfenati, A new hybrid system of QSAR models for predicting bioconcentration factors (BCF), Chemosphere 73 (2008) 1701–1707

hydroquinone in the category datasets. This makes the use of category/read-across options very uncertain for DAHQ as it is not possible to verify a prediction against a structure with the same functional group.
Therefore the category approach provided by the Registrant(s) is not considered by ECHA to be adequate for risk assessment or PBT assessment

At present there is insufficient information on bioaccumulation. However, the log Kow of the substance is uncertain, and it is noted that there is an adaption to the standard information requirement if the log Kow <3. Therefore the requirement will depend on the new log Kow measurement:

- If the new test determines the log Kow to be ≥4.5, and if the substance is determined to be P or vP from test 6 (simulation biodegradation test), the fish bioaccumulation test is requested.If the new test determines the log Kow to be between 3.0 and <4.5, the Registrant(s) shall update their environmental risk assessment using this value. If there is a secondary poisoning risk indicated, they shall perform the fish bioaccumulation study to refine the risk.If the new test determines the log Kow to be <3.0, no test on bioaccumulation is required.

Similar to the environmental simulation testing, the Registrant(s) argue that this test is not necessary as the log Kow indicates the substance does not screen as B/vB. As stated above under section III.A.2, ECHA is not satisfied that the available weight of evidence for log Kow demonstrates with confidence that the chemical can be excluded as screening as B/vB.

In their comments the Registrant(s) suggest that the reliability of log Kow diminishes above 6. It is not fully clear to ECHA the relevance of this comment to DAHQ (where the Registrant(s) claim a log Kow of 3.3); however, ECHA disagrees with the context of the comment that no substantial bioconcentration is assumed for compounds for log Pow greater than 6. ECHA agrees that it is generally accepted that BCF values from an aqueous fish bioconcentration test may decrease with increasing log Kow above 6, for instance the REACH R11 PBT guidance (p55) states that at log Kow >6 "a decreasing relationship between [log Kow and BCF] is seen". However this does not mean a log Kow > 6 cannot safely be used to exclude a substance from PBT assessment (i.e. as not B/vB). ECHA highlights that bioaccumulation exclusion criteria includes a (calculated) log Kow value >10 which is significantly higher than 6. There are a number of examples of chemicals with log Kow >6, which have been determined as being either B or vB based on bioaccumulation data.

In the opinion of ECHA a decision on whether DAHQ screens as B/vB or not cannot be made with confidence until a new log Kow study has been performed.

Therefore, pursuant to Article 46(1) of the REACH Regulation, and depending on the results of the requested partition coefficient study (request 2) and simulation biodegradation test (request 6), the Registrant(s) are required to carry out the following study using the registered substance subject to this decision:
Bioaccumulation in fish: Aqueous and Dietary Exposure test (OECD 305).

8. PBT assessment of all relevant impurities present in the registered substance at quantities at or above 0.1% w/w

The current registration does not include a PBT assessment of the impurities in the substance. At present ECHA is concerned that the impurities also screen as PBT or vPvB, as structurally they are very similar to DAHQ. A PBT assessment of all impurities present in the registered substance at quantities at or above 0.1% w/w is required. In completing this assessment, the Registrant(s)(s) shall refer to ECHA: *Guidance on information requirements*

and chemical safety assessment, Chapter R.11: PBT Assessment.

In their comments the Registrant(s) agreed to this request.

Therefore, pursuant to Article 46(1) of the REACH Regulation the Registrant(s) are required submit the following information regarding the registered substance subject to the present decision: PBT assessment of all relevant impurities.

B. Environmental exposure concerns

9. Adsorption-desorption

The need for this test depends on the result of the requested partition coefficient study (request 2).

The endpoint for adsorption/desorption in the registration dossier is fulfilled by the HPLC screening method (OECD 121 test guideline). The concern for log Kow, measured by HPLC, suggests uncertainty for the log Koc as this was measured using the same method. Koc is a key parameter for the fate of a chemical in the environmental risk assessment, so it is important to be certain about its value.

On this basis if the new measured log Kow value (request 2), measured using the slow-stir method, is not in agreement with the log Kow value measured by HPLC, a new absorption-desorption study (OECD 106) is required. If the new measured log Kow value, measured using the slow-stir method, is in agreement with the log Kow value measured by HPLC, no further data for log Koc are required.

In their comments the Registrant(s) argue that this test is not necessary as a reliable study exisits for the endpoint, and the recent pKa data shows that the substance was not ionised in the test. ECHA agrees that the new pKa data indicates that DAHQ would not be ionised under the conditions of the test. However as described above, there remain doubts about the log Kow value measured using the HPLC method. Until that is resolved, doubts also exist for the HPLC approach to derive a reliable Koc value, as the test relies on the same methodology.

Therefore, pursuant to Article 46(1) of the REACH Regulation, and depending on the result of the requested partition coefficient study (request 2), the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Adsorption – desorption using a batch equilibrium method (OECD 106).

10. Provide monitoring of DAHQ in effluent being discharged to municipal sewer at production site.

The Registrant(s) estimated the effect of various on-site effluent treatments to determine the concentration of DAHQ in the effluent discharged to the municipal sewer at the manufacturing lifecycle stage. There are a series of factors that reduce the emission to wastewater, but it is unclear how these values were verified.

Unless the Registrant(s) can provide justification for each of the emission reductions applied in the CSR, site-specific monitoring of DAHQ at the manufacturing site is required to substantiate the level of reductions claimed and the levels in the final effluent sent to sewer. If site specific monitoring is required, the Registrant(s) shall follow the advice detailed in REACH guidance R16, section 16.4. Samples shall be taken concurrently from both the influent and effluent for each wastewater treatment stage where an emission reduction has been applied, or alternatively at the initial influent and the final effluent stage. The fate of any non-aqueous phase such as liquid organic portion, or sludge shall also be detailed in the

CSR. The number of samples and period of sampling shall be statistically justified by the Registrant(s). The Registrant(s) shall also ensure that a suitably accurate substance-specific analytical method is used. The limit of detection shall be justified by the Registrant(s).

Alternatively, the Registrant(s) should assume the treatments have no effect and model the emissions accordingly.

In their comments the Registrant(s) agreed to this request.

Therefore, pursuant to Article 46(1) of the REACH Regulation the Registrant(s) are required submit the following information regarding the registered substance subject to the present decision: Monitoring of DAHQ in effluent being discharged to municipal sewer at production site.

C. Summary of the tiered test strategy

A proposal for amendment was submitted suggesting to include a table in the decision to provide clarity on the tiered test strategy. ECHA agrees that this is helpful, and has included one below. This summarises the conditions under which the tests 1-9 in the decision are required.

To summarise the tiering in the environmental test strategy:

<table>
<tr><th>Test requested</th><th colspan="3">Conditions when to perform tests 1-9 requested in the decision</th></tr>
<tr><td>Water solubility (test 1)</td><td colspan="3">Not applicable</td></tr>
<tr><td rowspan="6">Partition coefficient Kow (test 2)</td><td>If Kow<3</td><td>No further testing needed</td><td></td></tr>
<tr><td rowspan="2">If Kow ≥4.5</td><td rowspan="2">Perform simulation test (test 6)</td><td>If Persistent/very persistent, perform bioaccumulation study (test 7)</td></tr>
<tr><td>If not Persistent/very persistent, no further testing (unless secondary poisoning risk indicated)</td></tr>
<tr><td rowspan="2">If 3≤ Kow<4.5</td><td rowspan="2">Refine risk assessment</td><td>If no secondary poisoning risk, no further test needed</td></tr>
<tr><td>If secondary poisoning risk, perform bioaccumulation study (test 7)</td></tr>
<tr><td>If new Kow value in agreement to Kow derived from HPLC method (Kow=3.3)</td><td colspan="2">No further testing for adsorption-desorption</td></tr>
<tr><td>If new Kow value <u>not</u> in agreement to Kow derived from HPLC method (Kow=3.3)</td><td colspan="2">Perform adsorption-desorption test (test 9)</td></tr>
</table>

Long term Daphnia (test 3)	If NOEC<0.01 mg/L	Not P, not B	Perform **FELS (test 4)** for PNEC derivation
		P, B	No further testing
	If NOEC>0.01 mg/L	Not P, not B	Perform **FELS (test 4)** for PNEC derivation
		P, B	Perform **FELS (test 4)** to clarify T criterion
Algae (test 5)	Not applicable		

D. Additional concerns relating to human health

11. Local Lymph node Assay (LLNA)

The only information available in the dossier on skin sensitisation potential is a Human Repeat Insult Patch Test (HRIPT) which found positive skin reactions at induction and challenge. Skin reactions reported were generally isolated instances on one day of the challenge phase, however, the authors noted skin reactions consistent with skin sensitisation in 2/53 of the volunteers. The Registrant(s) consider the HRIPT to be negative, given the low incidence of skin sensitization responses, and the prevalence of skin irritation. Taking account of the potential for exposure there is a need to have a robust assessment of skin sensitisation potential. The mouse local lymph node assay (LLNA) is considered the most appropriate study to address this concern.

In their comments the Registrants agreed to this request.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Skin sensitisation: Local Lymph node Assay (OECD 429).

12. Information to support the DNEL derivation

a) Relevant historical control rates for thyroid effects observed in the 90-day rat study

b) Any available evidence to support the Mode of Action for induction of thyroid toxicity and human health relevance

The Registrant(s) used a NOAEL derived from a standard rat developmental toxicity study, of 70 mg/kg/day as the basis for their DNEL calculation. However, a NOAEL of 15 mg/kg/day derived from a 90-day oral repeated-dose study is considered to be a more appropriate point of departure to base risk characterisation on.

In the 90-day study, DAHQ caused a marked increase in the incidence of thyroid follicular cell hypertrophy, in both males and females, at doses of 50 mg/kg/day and above. There is no information presented to inform on a possible mode of action. Therefore, the observed thyroid changes cannot be dismissed as not being relevant for human health. A NOAEL of 15 mg/kg/day is therefore proposed for risk characterisation.

The Registrant(s) consider that the incidence of thyroid follicular cell hypertrophy is within the relevant historical rates. They have identified a NOAEL of 150 mg/kg/day, the highest dose tested, and therefore have not used this study for DNEL derivation. However, the study report does not contain any historical control data to support this opinion. An internet search for relevant historical control information (Charles River Hannover strain) did not find any evidence to support the Registrant(s)' view. The Registrant(s) are therefore required to

justify selection of the rat developmental toxicity study, rather than the 90-day repeated exposure study as the critical study for DNEL derivation. Provision of historical control data would enable an assessment of the Registrant(s) argument that the 90-day study should not be used for DNEL derivation.

In the original draft decision sent to the Registrant(s) for comments, the request was for justification for the key study and NOAEL used to determine the DNEL. In their comments the Registrant(s) restated that they did not consider using the NOAEL of 15 mg/kg/day from the 90-day repeated-dose rat study to be appropriate for DNEL derivation. They reaffirmed their opinion that the thyroid changes are within the relevant historical rates, but did not provide any information to support this. Additionally, they proposed that the thyroid changes may be secondary to liver enlargement, and that such changes are not relevant for human health. However, no additional information has been provided to support the proposed mode of action.

ECHA maintains that without historical control information for thyroid follicular hypertrophy or convincing evidence to support the proposed mode of action, the relevant NOAEL for DNEL derivation is 15 mg/kg/day from the 90-day study. The decision was revised to include a request for historical control data for the thyroid changes observed in the 90-day rat study, and information to support the proposed Mode of Action.

c) The Registrant(s) used the ECETOC guidance rather than the ECHA guidance (ECHA Guidance on Information Requirements and Chemical Safety Assessment, chapter R.8) for setting the DNEL values. Due to the different assessment factors applied, using the REACH guidance results in a lower DNEL than that derived by the Registrant(s). This affects the risk characterisation where risk characterisation ratios (RCRs) >1 are found for a significant number of exposure scenarios. In the original draft decision sent to the Registrant(s) for comments, the request was for justification of their selection of assessment factors used in the DNEL derivation. In their comments the Registrant(s) proposed to revise their DNEL derivation using the REACH guidance and therefore the request was changed to reflect this.

Therefore, pursuant to Article 46(1) of the REACH Regulation the Registrant(s) are required submit the following information regarding the registered substance subject to the present decision: Information to support the DNEL derivation, more specifically, a) relevant historical control rates for thyroid effects observed in the 90-day rat study, b) any available evidence to support the Mode of Action for induction of thyroid toxicity and human health relevance and c) revision of the DNEL derivation using the REACH guidance.

13. Information on suitable glove materials, thicknesses and breakthrough times

Although the Registrant(s) have identified a need to wear gloves, currently no information has been provided in the registration on suitable glove materials, required glove thickness and breakthrough times. This information should be provided in safety data sheets to help downstream users identify the most appropriate protective equipment to use when handling this substance.

In their comments the Registrant(s) agreed to this request.

Therefore, pursuant to Art 46(1) of the REACH regulation, the Registrant(s) are required to submit the following information regarding the registered substance subject to the present decision: information on suitable glove materials, required glove thicknesses and breakthrough times.

14. Further information on worker exposure

Using the DNELs calculated by the evaluating Member State RCRs > 1 are obtained for several contributing scenarios. If precautionary assumptions have been made in the exposure assessment, the risks in practice may be lower than these calculations suggest. However, from the information provided in the CSR, it is not clear whether the modelling parameters are based on precautionary or default assumptions or have been based on process specific information communicated to the Registrant(s) by downstream users. If the Registrant(s) modify their DNEL calculations in response to point 12 in the present decision, it will be necessary for them to revisit their exposure assessment to confirm that the operating conditions and risk management measures remain sufficient to ensure safe use. If the Registrant(s) choose to retain their current DNELs, in order to confirm that the risks to health are adequately managed by the measures recommended by the Registrant(s), it will be necessary to have further information about the conditions under which DAHQ is used such as the range of possible in use concentrations for each scenario and the likely duration for various tasks. Even if the Registrant(s) do modify their exposure assessment, it will be helpful if this information can be provided for the revised assessment.

In their comments the Registrant(s) agreed to this request.

Therefore, pursuant to Art 46(1) of the REACH regulation, the Registrant(s) are required to submit the following information regarding the registered substance subject to the present decision: further information on the operating conditions that are anticipated where TPHQ is used and an indication of whether the parameters that have been used to model exposures are based on assumptions or information communicated by downstream users.

Note to the Registrant(s): The Registrant(s) should ensure that any relevant results of the further testing/information requested in this decision are taken into account in any refinements of the exposure assessment.

E. Deadline for submitting the required information

In the draft decision communicated to the Registrant(s) the time indicated to provide the requested information was 30 months from the date of adoption of the decision. A proposal for amendment was submitted suggesting to extend the deadline for the Registrant(s) to provide the data requested in the decison to 48 months as the time did not appear to be sufficient. The Registrant made no comment on this proposal for amendment. The deadline has been extended in the case that a simulation biodegradation test (OECD 309) (request 7) is required.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental stud(y/ies), the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the test(s) must be shared by the Registrant(s).

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within

three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[4] by Leena Ylä-Mononen, Director of Evaluation

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

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