# SUBSTANCE EVALUATION CONCLUSION

## as required by REACH Article 48

## and

## EVALUATION REPORT

**for**

# Hydroquinone

**EC No 204-617-8**

**CAS No 123-31-9**

**Evaluating Member State(s):** Italy

Dated: 17 October 2017

# Evaluating Member State Competent Authority

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## Year of evaluation in CoRAP: 2012

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

**Further information on registered substances here:**

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

# Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

# Contents

# Part A. Conclusion

## 1. CONCERN(S) SUBJECT TO EVALUATION

Hydroquinone was originally selected for substance evaluation in order to clarify concerns about:

- Human health/CMR;
- Exposure/Wide dispersive use, consumer use, high aggregated tonnage;
- Risk characteriastion ratios close to 1 (human health).

During the evaluation also other concerns were identified. The additional concerns were:

- Acute and sub chronic inhalation exposure for workers during manufacturing and batching processing;
- A risk characteriastion ratios close to 1 (environment) and potential long term effects on aquatic compartment (environment).

## 2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable.

## 3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

**Table 1**

| CONCLUSION OF SUBSTANCE EVALUATION<br><br>Conclusions | Tick box |
|---|---|
| Need for follow-up regulatory action at EU level | X |
| Harmonised Classification and Labelling | X |
| Identification as SVHC (authorisation) | |
| Restrictions | |
| Other EU-wide measures | |
| No need for regulatory follow-up action at EU level | |

## 4. FOLLOW-UP AT EU LEVEL

### 4.1.1. Harmonised Classification and Labelling

The outcome of the long-term toxicity test on fish confirmed the ecotoxicological properties of the substance and its degradation product p-benzoquinone for the aquatic compartment. The data provided indicates that Hydroquinone is very toxic to aquatic life with long lasting effects, accordingly the substance was self- classified as Aquatic Chronic 1, with M-Factor 1.
eMSCA supports the additional hazard class of Aquatic Chronic 1, which however is not reflected in the current harmonised Hydroquinone classification for the environment, that is Aquatic Acute 1.

The proposed self-classification for the chronic toxicity is only a small percentage (less than 1%) than the number of self-classification from the notifications, leading to an uneven hazard profile of the substance. Therefore, a harmonised environmental classification is envisaged as a follow-up at Community level, which would be of priority and added value to the substance.

The other initial concerns can be removed, following the new information provided by the Registrans.

The new available data submitted by the registrant(s) on genotoxic potential of HQ (*in vivo* comet and TGR assays) indicates that the test substance does not appear to induce neither gene mutations nor DNA damage *in vivo*. In consideration of the positive results reported in micronucleus assays in rodent bone marrow, an aneugenic activity (that would not be detected by comet or TGR assays) cannot be excluded. However, it should be noted that aneugenicity does not imply direct interaction with DNA and can be caused by a thresholded mechanism of action [Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment, EFSA Journal 2011;9(9):2379].
In view of the experimental results reported in both *in vitro* and *in vivo* genotoxicity tests, a role of aneugenicity in the etiology of the tumors cannot be excluded. However, considering that this MoA is assumed to have a threshold, a DNEL for threshold effects can be derived for the risk assessment and a more severe classification is not justified.
Therefore, no further information are needed to clarify the hazard assessment on mutagenicity and carcinogenicity.

The Registrants provided all the elements to assess the environmental exposure estimation of the substance, as requested by ECHA. In particular, the life cycle tree of the substance has been re-evaluated: some exposure scenarios for professional use were not any longer sustainable by the Registrants and were therefore removed from the dossier, the assessment of the others gave no risk for environmental compartments. Moreover, an adequate justification for the use of non-default values for the environmental exposure estimation was provided.

# 5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

## 5.1. No need for regulatory follow-up at EU level

# 6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

The eMSCA has the intention to prepare an Annex XV dossier with a proposal for harmonized classification and labelling. The intention will be included in the RoI tentatively by the second half of 2019.

# Part B. Substance evaluation

# 7. EVALUATION REPORT

Hydroquinone is classified as Carc 2 and Muta 2. The current classification for carcinogenicity is based on renal tubule adenomas in male rats, mononuclear cell leukemias in female rats, hepatocellular adenomas in female mice and liver adenomas in male mice. The classification for Muta 2 is based on positive results in somatic cells and germ cells of animals. Even if there is some doubt concerning the relevance to humans of the observed renal tumors in male rats, the possibility that the different types of tumors in two species may be induced by a genotoxic mechanism cannot be completely ruled out.

The evaluating MSCA (eMSCA) requested to refine the derivation of the DNEL values for systemic and local effects for workers and consumers. Exposure to workers is likely during the manufacturing process and during batching. Professional users and consumers at photographic processing are also at risk for exposure. The RCRs reported by the registrant(s) were close to or equal to 1 for certain processes. In consideration of this latter point it is important to highlight that most of the exposure scenarios developed are complex and consist in several PROCs. The inhalation concentrations have been calculated separately for each PROC, however it is possible that some of the tasks that are described in the registration dossiers occur simultaneously. In this case it could be appropriate to consider the contribution of the different tasks to the actual exposure and to refine the RMMs in case of RCRs showing a non adequate control of risk.

In the course of the evaluation, the eMSCA noted additional concerns for the environment due to the long term effects on aquatic compartment. A further investigation on the chronic effects on fish, the most sensitive species in the available acute studies, was required in order to clarify the ecotoxicological profile of the substance and to verify whether there remains an uncontrolled risk to the environment that should be subjected to further risk management measures.

In the course of the evaluation, the eMSCA also noted additional concerns regarding a risk characterisation ratio for soil compartment close to 1. A refinement of the CSA process was requested in order to improve exposure levels and/or quantitative hazard information. The eMSCA recommended to include the assessment of the professional use, that was lacking in the dossier. Moreover, in the opinion of the eMSCA no adequate justification was provided for using non-default values in assessing the exposure estimation of the substance. All the above information were required in order to verify if the RCRs for all the environmental compartment were below one.

In consideration of the wide use of the substance the Italian Competent Authority required the dossier to be updated in order to take into account the concern expressed above with the aim to control the exposure scenarios presented in the registrations in order to ensure their effectiveness in protecting human health and the environment.

## 7.1. Overview of the substance evaluation performed

Hydroquinone was originally selected for substance evaluation in order to clarify concerns about:

- Human health/CMR;
- Exposure/Wide dispersive use, consumer use, high aggregated tonnage;
- Risk characterisation ratios close to 1 (human health).

During the evaluation also other concerns were identified. The additional concerns were:

- Acute and sub chronic inhalation exposure for workers during manufacturing and batching processing;
- A risk characteriastion ratio close to 1 (environment) and potential long term effects on aquatic compartment (environment).

**Table 3**

| **EVALUATED ENDPOINTS** | |
|---|---|
| **Endpoint evaluated** | **Outcome/conclusion** |
| *Endpoint 1*<br>A Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (TGR) in rats treated via oral administration during 28 consecutive days (test method: OECD 488)<br><br>Alternatively,<br><br>an *in vivo* comet assay, according to experimental protocols currently agreed at international level (e.g. "*SCIENTIFIC REPORT OF EFSA, Minimum Criteria for the acceptance of in vivo alkaline Comet Assay Reports*" [2], Tice *et al*. (2000) [3] and Hartmann *et al*. (2003)[4], see also ECHA guidance[5],) could be considered acceptable. The Comet assay shall be performed in rats by oral administration on the same target cells. | Requests fulfilled by the registrants.<br>No further action is needed. |
| *Endpoint 2*<br>Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: B.29/OECD 413) unless the Registrant(s) demonstrate that testing is | Requests fulfilled by the registrants since the justification for waiving the study for the purpose of this substance evaluation is considered acceptable. |

[2]"SCIENTIFIC REPORT OF EFSA, Minimum Criteria for the acceptance of in vivo alkaline Comet Assay Reports" (LINK: http://www.efsa.europa.eu/en/efsajournal/doc/2977.pdf)

[3] Tice RR, Agurell E, Anderson D, Burlinson B, Hartmann A, Kobayashi H, Miyamae Y, Rojas E, Ryu JC, Sasaki YF. Single cell gel/comet assay: guidelines for in vitro and in vivo genetic toxicology testing. Environ Mol Mutagen, 2000, 35(3):206-21.

[4] Hartmann A, Agurell E, Beevers C, Brendler-Schwaab S, Burlinson B, Clay P, Collins A, Smith A, Speit G, Thybaud V, Tice RR. Recommendations for conducting the in vivo alkaline Comet assay. Mutagenesis, 2003, Jan;18(1):45-5.

[5] Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.7.1, Mutagenicity, Version 2.0, November 2012.

| | |
|---|---|
| not feasable due to the explosiveness of the dust in testing preparation. | No further action is needed. |
| *Endpoint 3*<br>Long-term toxicity on fish taking into account the OECD Guidance document on aquatic toxicity testing of difficult substances and mixtures | Requests fulfilled by the registrants, the data provided indicates that HQ is very toxic to aquatic life with long lasting effects. Harmonised C&L is proposed as a follow-up at EU level. |
| *Endpoint 4*<br>Effects on soil micro-organism | Requests fulfilled by the registrants.<br>No further action is needed. |
| *Endpoint 5*<br>Long-term toxicity testing on soil invertebrates and plants | Requests fulfilled by the registrants since the justification for waiving the study for the purpose of this substance evaluation is considered acceptable.<br>No further action is needed. |
| *Endpoint 6*<br>Environmental exposure assessment and the risk characterization for all the identified professional uses | Requests fulfilled by the registrants.<br>No further action is needed.<br>The life cycle tree has been reassessed by the registrants and some ESs for professional use were no longer sustainable and were therefore removed from the dossier. |
| *Endpoint 7*<br>Justification for the non-default use of some values (dilution factor river; effluent discharge of STP; regional releases) | Requests fulfilled by the registrants.<br>No further action is needed. |
| *Endpoint 8*<br>Exposure assessment to agricultural soil | Requests fulfilled by the registrants.<br>No further action is needed.<br>Exposure information on soil compartment were provided. For ES3, ES7, ES8, ES9 and the combined local exposure from ES2 and ES3, the derived RCRs for freshwater, sediment (freshwater), marine water and sediment (marine water) are below 1, but close to it. (see discussion in section 7.12 and 7.13) |
| *Endpoint 9*<br>Exposure assessment for all relevant exposures including development of respective exposure scenarios. | Requests fulfilled by the registrants.<br>No further action is needed. |
| *Enpoint 10*<br>The registrants are requested to carefully justify the route to route extrapolation from oral route to dermal/inhalation routes. | Requests fulfilled by the registrants.<br>No further action is needed. |

## 7.2. Procedure

The Substance evaluation of the Hydroquinone has started on February 2012.
The evaluating MSCA considered that further information was required to clarify the above mentioned 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 28 February 2013.
After discussion in the Member State Committee meeting on 3-7 February 2014, a unanimous agreement of the Member State Committee on the draft decision as modified

at the meeting was reached on 7 February 2014. ECHA took the decision on 16 May 2014 pursuant to Article 51(6) of the REACH Regulation.
eMSCA had interactions with the Registrant and following that interactions, the Registrant have made dossier updates and eMSCA took into account the updated dossiers.

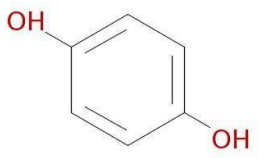
## 7.3. Identity of the substance

**Table 4**

| SUBSTANCE IDENTITY | |
|---|---|
| **Public name:** | Hydroquinone |
| **EC number:** | 204-617-8 |
| **CAS number:** | 123-31-9 |
| **Index number in Annex VI of the CLP Regulation:** | 604-005-00-4 |
| **Molecular formula:** | C6H6O2 |
| **Molecular weight range:** | --- |
| **Synonyms:** | --- |

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

**Structural formula:**




## 7.4. Physico-chemical properties

**Table 5**

| OVERVIEW OF PHYSICOCHEMICAL PROPERTIES | |
|---|---|
| **Property** | **Value** |
| Physical state at 20°C and 101.3 kPa | white crystalline solid |
| Vapour pressure | 1.33 hPa at 132.4 °C |
| Water solubility | very soluble (> 10000 mg/L) |
| Partition coefficient n-octanol/water (Log Kow) | 1.03 at 25 °C |
| Flammability | hydroquinone can not be considered as highly flammable |
| Explosive properties | Data waiving |

| | |
|---|---|
| Oxidising properties | Data waiving |
| Granulometry | The X10, X50, and X90 values were determined to be 136.4, 286.0, and 478.8 µm for the extra pure quality and 125.8, 281.0, and 481.8 µm for the premium quality, respectively. The amount of fines <100 µm were found to be 4 (extra pure) and 5% w/w (premium) and the classes of particles < 105 µm were determied to be 4.4 (extra pure) and 5.95% in volume (premium) |
| Stability in organic solvents and identity of relevant degradation products | Data waiving |
| Dissociation constant | According to the data from this peer-reviewed database, the pKa for hydroquinone is 10.85 or 9.96 according to two different original sources. |

## 7.5. Manufacture and uses

### 7.5.1. Quantities

**Table 6**

| AGGREGATED TONNAGE (PER YEAR) | | | | |
|---|---|---|---|---|
| ☐ 1 – 10 t | ☐ 10 – 100 t | ☐ 100 – 1000 t | ☐ 1000- 10,000 t | ☒ 10,000-50,000 t |
| ☒ 50,000 – 100,000 t | ☐ 100,000 – 500,000 t | ☐ 500,000 – 1000,000 t | ☐ > 1000,000 t | ☐ Confidential |

On ECHA dissemination website the aggregated tonnage reported is 10 000 -100 000 t/a.

### 7.5.2. Overview of uses

This substance is used in the following products: photo-chemicals, polymers, coating products, inks and toners and water treatment chemicals. This substance has an industrial use resulting in manufacture of another substance (use of intermediates).
This substance is used in the following areas: printing and recorded media reproduction and formulation of mixtures and/or re-packaging. This substance is used for the manufacture of chemicals and plastic products.
Release to the environment of this substance is likely to occur from industrial use: as processing aid, as an intermediate step in further manufacturing of another substance (use of intermediates), formulation of mixtures and for thermoplastic manufacture.
ECHA has no registered data indicating whether or into which articles the substance might have been processed.

**Table 7**

| USES | Use(s) |
|---|---|
| **Uses as intermediate** | -- |
| **Formulation** | Formulation into mixture, formulation for photographic processing (liquid and solid), formulation in water treatment mixtures (solid in a liquid). |
| **Uses at industrial sites** | Photographic Processing (Photographic industry)<br>Use as monomer<br>Stabilizer for Ink and Coatings (CEPE, ESVOC)<br>Formulation, Distribution, Storage<br>Use as stabilizer additive in Polymers and Rubbers - moulding applications (PEST)(ETRMA)<br>Use as process additive - inhibitor I (polymerization prevention, continuous process)<br>Use as process additive - inhibitor II (polymerization prevention, batch process)<br>Industrial use as oxygen scavenger<br>Manufacture of hydroquinone and Use as chemical Intermediate |
| **Uses by professional workers** | Use as stabilizer additive in Polymers and Rubbers - moulding applications (PEST)(ETRMA)<br>Stabilizer for Ink and Coatings (CEPE, ESVOC)<br>Photographic Processing (Photographic industry) |
| **Consumer Uses** | Photographic Processing (Photographic industry)<br>Use in photographic processing |
| **Article service life** | --- |

## 7.6. Classification and Labelling

### 7.6.1. Harmonised Classification (Annex VI of CLP)

The substance is currently listed on Annex VI of CLP Regulation ((EC) No 1272/2008).

**Table 8**

| HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008) | | | | | | |
|---|---|---|---|---|---|---|
| **Index No** | **International Chemical Identification** | **EC No** | **CAS No** | **Classification** | **Spec. Conc. Limits, M-factors** | **Notes** |
| | | | | **Hazard Class and Category Code(s)** | **Hazard statement code(s)** | |
| 604-005-00-4 | 1,4-dihydroxybenzene hydroquinone quinol | 204-617-8 | 123-31-9 | Acute Tox. 4 (H302)<br>Eye Dam. 1 (H318)<br>Skin Sens. 1 (H317)<br>Muta. 2 (H341)<br>Carc. 2 (H351)<br>Aquatic Acute 1 (H400) | H302<br>H318<br>H317<br>H341<br>H351<br>H400 | M=10 |

### 7.6.2. Self-classification

- In the registration(s) the following hazard classes are present in addition to the harmonised classification:

| | |
|---|---|
| Aquatic Chronic 1 | H410 (M-Factor: 1) |
| Skin Sens. 1B | H317 |

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

| | |
|---|---|
| Acute Tox. 4 | H312 |
| Skin Irrit. 2 | H315 |
| Acute Tox. 3 | H301 |
| Muta. 1B | H340 |
| Repr. 1B | H360 |
| STOT SE 1 | H370 (data lacking) |
| STOT RE 1 | H372 (data lacking) |

## 7.7. Environmental fate properties

### 7.7.1. Degradation

Concerning abiotic degradation, Hydroquinone is photo-oxidized in water forming p-benzoquinone, hydroxy-p-benzoquinone and trihydroxybenzene as products. A half-life of 20 h is estimated.

Hydroquinone proved to be readily biodegradable according to OECD 301C (70% biodegradation after 14d). Under aerobic condition, p-benzoquinone, hydroxy-p-benzoquinone and β-ketoadipic acid were identified as metabolic intermediates.

Based on the available information, the eMSCA can support the conclusion on this endpoint.

### 7.7.2. Environmental distribution

Based on distribution modelling, due to its physicochemical properties (low sorption to organic matter, high water solubility, low vapour pressure), Hydroquinone is expected to be found predominantly in the aquatic compartment. The eMSCA can support the Registrants' conclusion on this endpoint.

### 7.7.3. Bioaccumulation

Hydroquinone showed a low octanol water partition coefficient (log Kow = 0.59) and a BCF of 3.162 L/kg was estimated, therefore a low bioaccumulation of the substance is expected.

Based on the available information, the eMSCA can support the conclusion on this endpoint.

## 7.8. Environmental hazard assessment

### 7.8.1. Aquatic compartment (including sediment)

#### 7.8.1.1. Fish

Short-term toxicity

Three short-term toxicity studies with two freshwater species were provided by the Registrants, but only the study with *Oncorhynchus mykiss*, that showed a 96h LC50 of 0.638 mg/L (measured concentration), was considered reliable.

However, the eMSCA considered acceptable the study on the acute toxicity of Hydroquinone to *Pimephales promelas*. A reliable 96h LC50 of 0.044 mg/L was determined that represents the lowest value available for this endpoint and can be used for the purpose of CSA.

Long-term toxicity

In the final Substance Evaluation decision under Section III at point 3, the Registrants were required to carry out long-term toxicity testing on fish (OECD 210) in order to clarify the ecotoxicological profile of the substance and its degradation product, and to refine the PNEC of the aquatic compartment and related risk characterization.

The Registrants submitted a Fish early-life stage toxicity test, according to OECD 210, under flow-through conditions and the GLP. The study was performed with *Pimephales promelas* for a total exposure duration of 32 days. Five Hydroquinone concentrations were tested and samples for chemical analysis were taken during the test. The measured concentrations didn't remain within 80-120% of the nominal concentrations. The contributions of the degradation product p-benzoquinone were also measured. The degradation product concentration varied and a decrease of its contribution was observed as test item concentration increased. At the highest target concentration of Hydroquinone (100 µg/L, nominal), its contribution was between 8 and 19% relative to the measured Hydroquinone concentration of 66 µg/L. However, because of the rapid interconversion between Hydroquinone and p-benzoquinone in samples, the real concentration of both substances was uncertain. The effects on embryonic survival, development and hatching, and on larval growth were observed. Hydroquinone didn't induce any significant, visible effects on these endpoints at the target concentrations up to the highest concentration of

100 µg/L, corresponding to the average measured concentration of 66 µg/L. Hence, a 32d NOEC of 100 µg/L (nominal) and a 32d NOEC of 66 µg/L (mean meas.) were provided.

Based on all available information, the eMSCA concludes that the submitted data are sufficient and suitable for CSA as well as for a definitive assessment of this endpoint.

Reliable results from Fish early-life stage study newly submitted by the Registrants can be used to definitively clarify the chronic hazard profile of Hydroquinone and its degradation product p-benzoquinone for the aquatic compartment.

Therefore, following the assessment, the eMSCA concludes that the additional data provided meet the request specified under Section III.3 of the Substance Evaluation decision and indicates that Hydroquinone is very toxic to aquatic life with long lasting effects. No further information is needed to clarify this endpoint and the related concern, however a harmonised environmental classification is envisaged as a follow-up at Community level, to take into account the chronic aquatic toxicity.

#### 7.8.1.2. Aquatic invertebrates

The Registrants reported several values for short-term toxicity to invertebrates, the lowest reliable value is a 48h LC50 of 0.134 mg/L (measured, initial) for Daphnia, according to test guideline OECD 202.

The chronic toxicity of the substance to invertebrates was based on the only long-term toxicity study provided by the Registrants. A 21d NOEC of 0.0057 mg/L (measured, initial) based on reproduction for Daphnia, according to test guideline OECD 211, was found. The chronic toxicity value was considered reliable and suitable for CSA and for the derivation of the aquatic PNECs.

Based on the available information, the eMSCA can support the conclusion on this endpoint.

No further information is needed to be required to clarify the hazard for aquatic invertebrates.

#### 7.8.1.3. Algae and aquatic plants

The effects of Hydroquinone on algae were based on a study with *Pseudokirchnerella subcapitata* according to test guideline OECD 201. The 72h ErC50 and NOEC (growth rate) were determinate to be 0.330 mg/L and 0.019 mg/L (measured, initial).

These results can be considered suitable and conclusive for the purpose of CSA.

Based on the available information, the eMSCA can support this conclusion and no further information on this endpoint is needed.

#### 7.8.1.4. Sediment organisms

The Registrants waived information on the effects on sediment organisms on the base of exposure considerations, in accordance with Column 2 of REACH Annex IX.

CSA was performed applying the Equilibrium Partitioning method (EPM) based on the available aquatic toxicity data.

Based on the available information, eMSCA concludes that the EPM approach is suitable for sediment hazard assessment on Hydroquinone.

#### 7.8.1.5. Other aquatic organisms

Not relevant for this evaluation.

## 7.8.2. Terrestrial compartment

As indicated in the substance evaluation decision under Section III at points 4 and 5, the Registrants were required to carry out short-term toxicity testing on soil micro-organisms (OECD 216) as well as long-term toxicity testing on soil invertebrates and plants (OECD 220 or 232; OECD 208 or ISO 22030) in order to further investigate the effects of the Hydroquinone on terrestrial organisms and, accordingly, to refine the PNEC soil and related risk characterization.

Toxicity to soil micro-organisms

The Registrants submitted a reliable soil micro-organisms toxicity study performed according to OECD 216 and under GLP.

The 28d EC10 and EC50 were determined at 19.5 and 60.1 mg/kg dry soil respectively and these values were used for the purpose of CSA. All validity criteria of the test were fulfilled. These submitted data were taken into account for the derivation of PNEC soil as well as for assessment of the toxicity on soil organisms.

eMSCA concludes that soil micro-organisms data can be considered suitable and definitive for this endpoint. Consequently, no additional information is required to clarify the related concern.

Toxicity to soil macro-organisms and terrestrial plants

Concerning the other terrestrial endpoints (soil invertebrates and plants) the Registrants considered that the required studies do not need to be conducted, according to REACH Annexes IX and X.

Therefore, a data waiving was confirmed, claiming exposure-based justifications. The Registrants declare that direct exposure to soil is considered unlikely in view of identified uses without intentional release of this substance in terrestrial compartment. In addition, the Registrants argue that indirect exposure to soil (via sewage sludge application and/or aerial deposition) is considered negligible, considering the physico-chemical and environmental fate properties (ready biodegradability, low adsorptive and bioaccumulative potential, very low volatility) as well as exposure pattern of the registered substance. According to the data provided in the registration dossier, eMSCA agrees with Registrants' conclusion that any significant direct and indirect exposure of soil compartment is unlikely to occur. Moreover, the outcome of refined CSA also indicates that no risk for soil compartment was identified (RCR values for agricultural soil below 0.2).

Therefore, following the assessment, eMSCA may conclude that data waiving arguments provided by the Registrants are acceptable and sufficient for CSA. No further toxicity testing on terrestrial organisms is needed to be performed.

## 7.8.3. Microbiological activity in sewage treatment systems

The respiration inhibition of activated sludge was provided by the Registrants and a 2h IC50 of 71 mg/L was determined.
This result can be considered suitable and conclusive for the purpose of CSA.
Based on the available information, the eMSCA can support this conclusion.

### 7.8.4. PNEC derivation and other hazard conclusions

**Table 9**

| PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS | | |
|---|---|---|
| **Hazard assessment conclusion for the environment compartment** | **Hazard conclusion** | **Remarks/Justification** |
| Freshwater | PNEC aqua (freshwater): 0.57 µg/L | Assessment factor: 10<br>Reliable long-term results from three trophic levels are available. According to ECHA guidance, an assessment factor of 10 can be applied to the lowest long-term result, that is a NOEC of 0.0057 mg/L obtained in the Daphnia reproduction test. |
| Marine water | PNEC aqua (marine waters): 0.057 µg/L | Assessment factor: 100<br>No information are available on the toxicity effects on saltwater species. An assessment factor of 100 can be applied to the lowest long-term result obtained from freshwater species covering three trophic levels, according to ECHA guidance. Therefore the NOEC of 0.0057 mg/L obtained in the Daphnia reproduction test is used to derive the PNEC value. |
| Intermittent releases to water | PNEC aqua (intermittent releases): 1.34 µg/L | Assessment factor: 100<br>According to ECHA guidance, an assessment factor of 100 can be applied to the lowest short-term result.<br>The Registrants derive the PNEC value using the EC50 of 0.134 mg/L obtained from the acute toxicity test with Daphnia.<br>The eMSCA proposes to consider the lowest acute toxicity result obtained for fish (LC50 = 0.044 mg/L), to derive a PNEC of 0.44 µg/L. |
| Sediments (freshwater) | PNEC aqua (sediment freshwater): 4.9 µg/kg sediment dw | Extrapolation method: equilibrium partitioning<br>In the absence of data on sediment organisms, the PNEC sediment may be calculated applying the EPM based on the PNEC aqua (freshwater). |
| Sediments (marine water) | PNEC aqua (sediment marine water): 0.49 µg/kg sediment dw | Extrapolation method: equilibrium partitioning<br>In the absence of data on sediment organisms, the PNEC sediment may be calculated applying the EPM based on the PNEC aqua (marine waters). |

| | | |
|---|---|---|
| Soil | PNEC soil: 0.64 µg/Kg soil dw | Extrapolation method: equilibrium partitioning<br><br>Only one terrestrial toxicity result is available on soil micro-organisms (EC50=60.1 mg/Kg soil dw).<br>According to ECHA Guidance R.10, in this case, both soil toxicity data available and EPM-modified aquatic toxicity data are used in deriving PNEC soil.<br>By applying an assessment factor of 1000 to the available soil toxicity value, the resulting PNEC soil is higher than the PNEC calculated via EPM.<br>Therefore, EPM-based PNEC soil value is considered sufficiently protective for terrestrial organism. |

PNEC aqua (intermittent releases)

Based on the reliable results of short-term toxicity data, the Registrants derived the PNEC aqua (intermittent releases) using the lowest EC50 of 0.134 mg/L obtained from the acute toxicity test with Daphnia, applying an assessment factor of 100, according to ECHA guidance.

The eMSCA considered acceptable the study on the acute toxicity of Hydroquinone to *Pimephales promelas.* A reliable 96h LC50 of 0.044 mg/L was determined that was usable for the purpose of CSA. Therefore, based on the lowest acute toxicity result, a PNEC of 0.44 µg/L was derived, applying an assessment factor of 100.

PNEC soil

The Registrants used a PNEC soil value of 0.64 µg/Kg soil dw derived by the equilibrium partitioning method (EPM).

Taking into account the only available terrestrial toxicity data (EC50 60.1 mg/Kg soil dw on soil micro-organisms), a PNEC soil value was also calculated using an assessment factor of 1000.

According to ECHA Guidance R.10, in this case, both the available soil data and EPM-modified aquatic toxicity data should be used to derive PNEC soil; then, by comparing both PEC/PNEC soil ratios, the highest one is chosen for risk characterization. In this case, EPM-based PNEC soil can be considered sufficiently protective for terrestrial toxicity and conclusive for soil risk characterization. The screening assessment performed through the EPM method based on aquatic toxicity data indicates no risk for soil compartment.

Based on the evaluation of relevant data submitted on Hydroquinone, eMSCA concludes that no further information is needed in order to clarify terrestrial hazard assessment and related risk characterization.

## 7.8.5. Conclusions for classification and labelling

According to the harmonised classification and labelling, Hydroquinone is very toxic to aquatic life with an acute M factor of 10. Additionally, the substance is readily

biodegradable and is not considered as bioaccumulable, on the base of chronic toxicity data this substance is very toxic to aquatic life with long lasting effects with a M factor of 1. Therefore, the environmental classification is:

Aquatic acute 1, H400 with M-Factor = 10;

Aquatic chronic 1, H410 with M-Factor = 1.

The conclusion on environmental classification is not reflected in the current harmonised classification, where only the acute aquatic toxicity is indicated. The proposed self-classification for the chronic toxicity is only a small percentage (less than 1%) than the number of self-classification from the notifications, leading to an uneven hazard profile of the substance. Therefore, a harmonised environmental classification is envisaged as a follow-up at Community level, which would be of priority and added value to the substance.

## 7.9. Human Health hazard assessment

### 7.9.1. Toxicokinetics

The toxicokinetics, metabolism and distribution of HQ have been comprehensively investigated in several key studies. The significant differences existing between animal species as well as between animals versus humans, and between strains of rats are crucial for the interpretation of the biological relevance of findings in animal studies, e.g. on repeated dose toxicity or genotoxicity, as well as for human risk assessment. Moreover, based on the findings of excretion of HQ and metabolites in urine of test persons without HQ exposure, or on background levels of HQ-derived protein-S-adducts in tissues of rats and mice, a considerable background exposure to HQ exists both in humans (Key studies: Deisinger, 1996; Deisinger et al., 1994) and in test animals (Key studies: Boatman et al., 1994, 2000a, b). This background exposure originates from dietary sources, from endogenous production, and from further uncharacterised sources.

PBPK models support route-to-route extrapolation using the findings in oral studies as a worst case approach for risk assessment.

**Value used for CSA:**
Bioaccumulation potential: no bioaccumulation potential
Absorption rate - oral (%): 100
Absorption rate - dermal (%): 10
Absorption rate - inhalation (%): 100

eMSCA can support these conclusions.

### 7.9.2. Acute toxicity and Corrosion/Irritation

The substance has an harmonised classification as Acute Tox 4* H302 and Eye Dam. 1 H318.

7.9.2.1 Acute toxicity inhalation

The registrant submitted data on a surrogate substance (isomer of HQ, structural analog) indicate an 8hr LC50 > 7.8 mg/L with no clinical signs. Based on the available information on particle size of HQ material, solubility, rapid systemic metabolisation after lung absorption following intratracheal administration, experimental inhalation data on a structurally similar substance, and weight of evidence including observations in the workplace, there is a low concern to humans for acute systemic toxicity and local effects under realistic exposure conditions in the workplace environment.

eMSCA supports these conclusions regarding acute toxicity inhalation.

7.9.2.2 Eye irritation/corrosion

The registrant produced a justification to cover the assessment of the eye irritating potential of HQ as HQ dust is known to produce severe irreversible eye injury in exposed workers.

eMSCA supports these conclusions.

## 7.9.3. Repeated dose toxicity: inhalation

The registrant produced the following justification for data waiving:

Because of the dust explosiveness properties shown with the product as manufactured (particle size > 100µm) as well as under standardised conditions (particle size > 63 µm), producing a micronised sample with the particle size distribution required by the test guidelines for a repeated dose inhalation study was not considered feasible under safe conditions. (Communication with ECHA and MSCA). However available information from other experimental animal studies (including other exposure routes) and human data available in the literature can provide information relevant to human exposure to airborne HQ and risk assessment.

Based on the available information from other experimental animal studies (including other exposure routes) and human data available in the literature, the eMSCA considers the concern with sub-chronic exposure for workers (by inhalation) during manufacturing and batching processing clarified.

No further information are needed to be required to clarify the concern for repeated dose toxicity.

## 7.9.4. Mutagenicity

Hydroquinone was negative in bacterial tests, while mutagenicity was reported in several in vitro studies on mammalian cells. In vivo genotoxicity in bone marrow and in germ cells was reported after i.p. administration. After oral administration, Hydroquinone produced a weak but significant induction of Micronucleus MN in bone marrow in animals treated by gavage but was negative when given in the diet. Hydroquinone did not induce lethal dominant mutation when administered by gavage but this test, rather obsolete and commonly considered of low sensitivity, was not sufficient to exclude an in vivo genotoxic potential of Hydroquinone in germ cells.

The new available data submitted by the registrant(s) are:

- A comet assay performed in rats after oral administration in duodenum, liver, kidney and male gonads
- A TGR in mouse by gavage in Liver, stomach, kidney, lung, and thyroid (Matsumoto M et al; Mutat. Res. Genet. Toxicol. Environ. Mutagen. 775-776:94-98; 2014).

Negative results were reported in both these in vivo studies, indicating that the test substance does not appear to induce neither gene mutations nor DNA damage *in vivo*.

In consideration of the positive results reported in micronucleus assays in rodent bone marrow, an aneugenic activity (that would not be detected by comet or TGR assays) cannot be excluded. However, it should be noted that aneugenicity does not imply direct interaction with DNA and can be caused by a thresholded mechanism of action [Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment, EFSA Journal 2011;9(9):2379].

Based on the criteria of the CLP Regulation (EC) 1272/2008, HQ has been classified to Germ cell mutagenicity category 2, H341 suspected of causing genetic effects (genotoxic effects observed in animal experiments with intraperitoneal or oral application).

Based on the available information, the eMSCA supports the conclusion on this endpoint.

No further information are needed to be required to clarify the concern for mutagenicity.

### 7.9.5. Carcinogenicity

HQ has been classified in Carcinogenicity Category 2 (suspected human carcinogen) according to C&L of the GHS based on the presence of renal tubular adenomas and hyperplasia in male Fischer F344 rats. Numerous mechanistic investigations have indicated that the likely mechanism is related to exacerbation of Chronic Progressive Nephropathy a pathology to which Fischer F344 male rats are particularly susceptible, possibly related to a higher kidney exposure to toxic metabolites in that rat strain, but not related to direct DNA damage nor to DNA adducts. This mechanism is supported by the lack of DNA binding activity in kidneys, and by negative results in in vivo TGR assay in mice and in vivo Comet assay in F344 rats.

In view of the experimental results reported in both *in vitro* and *in vivo* genotoxicity tests, a role of aneugenicity in the etiology of the tumors cannot be excluded. However, considering that this MoA is assumed to have a threshold, a DNEL for threshold effects can be derived for the risk assessment and a more severe classification is not justified.

Based on the available information, the eMSCA supports the conclusion on this endpoint.

No further information are needed to be required to clarify the concern for carcinogenicity.

### 7.9.6. Toxicity to reproduction (effects on fertility and developmental toxicity)

Not evaluated.

### 7.9.7. Hazard assessment of physico-chemical properties

Regarding the potential explosive properties of hydroquinone dust the available information, completed by monitoring data and exposure controls in place, recommended RPE (Respiratory Protection Equipment) for the most critical tasks, support the low concern under the current operating conditions. The eMSCA supports the conclusion on this enpoint.

## 7.9.8. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Following table shows the derivation of the DNELs for the relevant route of exposure for workers and general population provided by the registrant.

**Table 10**

| CRITICAL DNELS/DMELS | | | | | |
|---|---|---|---|---|---|
| **Endpoint of concern** | **Type of effect** | **Critical study(ies)** | **Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)** | **DNEL/ DMEL** | **Justification/ Remarks** |
| Inhalation Workers | Systemic effects - Acute | DNELs derived from the data from the carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 2.1 mg/m³ | Long term DNEL is considered protective for acute systemic effets |
| Inhalation<br>Workers | Systemic effects -<br>Long-term | Carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 2.1 mg/m³ | AF for other interspecies differences: 2.5<br>AF for intraspecies differences: 5<br>Overall Assessment Factor: 12.5 |
| Inhalation<br>Workers | Local effects -<br>Long-term | Carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 2.1 mg/m³ | Long-term systemic DNEL derived from the lowest BMDL10 value is considered protective of local effects. |
| Inhalation<br>Workers | Local effects -<br>Acute | Carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 2.1 mg/m³ | Long-term systemic DNEL derived from the lowest BMDL10 value is considered protective of local effects. |
| Dermal Workers | Systemic effects -<br>Long-term | Carcinogenicity (Oral) | BMDL10<br>150 mg/kg bw/day | 3.33 mg/kg bw/day | AF for interspecies differences (allometric scaling): 9<br>AF for intraspecies differences: 5<br>Overall Assessment Factor: 45 |

| | | | | | |
|---|---|---|---|---|---|
| Inhalation<br>General population | Systemic effects - Acute | DNELs derived from the data from the carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 1.05 mg/m³ | Long term DNEL is considered protective for acute systemic effets |
| Inhalation<br><br>General population | Systemic effects -<br><br>Long-term | Carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 1.05 mg/m³ | AF for other interspecies differences: 2.5<br><br>AF for intraspecies differences: 10<br><br>(Default value - ECHA guidance)<br><br>Overall Assessment Factor: 25 |
| Inhalation<br><br>General population | Local effects -<br><br>Long-term | Carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 1.05 mg/m³ | Long-term systemic DNEL derived from the lowest BMDL10 value is considered protective of local effects. |
| Inhalation<br><br>General population | Local effects -<br><br>Acute | Carcinogenicity (Oral) | Dose descriptor starting point: BMCL10 26.17 mg/m³ | 1.05 mg/m³ | Long-term systemic DNEL derived from the lowest BMDL10 value is considered protective of local effects. |
| Dermal<br>General population | Systemic effects -<br><br>Long-term | Carcinogenicity (Oral) | BMDL10<br><br>150 mg/kg bw/day | 1.66 mg/kg bw/day | AF for interspecies differences (allometric scaling): 9<br>AF for intraspecies differences: 10<br>(Default value for workers - ECHA guidance)<br><br>Overall Assessment Factor: 90 |
| Oral<br>General population | Systemic effects -<br><br>Long-term | Carcinogenicity (Oral) | BMDL10<br><br>15 mg/kg/day | 0.6 mg/kg bw/day | AF for interspecies differences (allometric scaling): 2.5<br>AF for intraspecies differences: 10<br>Overall Assessment Factor: 25 |

The eMSCA is in agreement with the registrant regarding the choice of assessment factors used in the derivation DNELs.
No further information are needed.

### 7.9.9. Conclusions of the human health hazard assessment and related classification and labelling

The conclusions of the assessment for human health hazard and taking into account the harmonised classification according to Regulation (EC) n. 1272/2008 are the following: the substance has an harmonised classification as Acute Tox 4* H302, Eye Dam. 1 H318 and Skin Sens 1 H317. Based on the available information on particle size of HQ material, solubility, rapid systemic metabolisation after lung absorption following intratracheal administration, experimental inhalation data on a structurally similar substance, and weight of evidence including observations in the workplace, there is a low concern to humans for acute systemic toxicity and local effects under realistic exposure conditions in the workplace environment.

## 7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

## 7.11. PBT and VPVB assessment

Persistence

The Registrants concluded that the substance is readily biodegradable and based on the available information, the eMSCA can support this conclusion.

Bioaccumulation

The Registrants concluded the substance is not bioaccumulative and based on the available information, the eMSCA can support this conclusion.

Toxicity

The Registrants concluded the substance is toxic to aquatic organisms, on the base of the lowest NOEC that was < 0.01 mg/L.

Overall conclusion

Taking into account the available information, although the substance fulfils the criteria for toxicity, the data indicate that Hydroquinone is neither fulfilling the criteria for persistence and bioaccumulation. Therefore, the eMSCA can support the Registrant conclusion that the substance is not PBT/vPvB.

## 7.12. Exposure assessment

The eMSCA agrees with the exposure calculations and with the operational conditions and risk management measures (RMMs) proposed by the registrant(s). Most of the exposure scenarios developed are complex and consist in several PROCs. The inhalation concentrations have been calculated separately for each PROC. However it is possible that some of the tasks that are described in the registration dossiers occur simultaneously. The appropriate contribute of the different tasks to the actual exposure were considered by the registrant(s). The efficacy of the RMMs proposed has been revised in light of these considerations and also in relation to a revision of the DNEL calculation.

The Registrants provided all the elements to assess the environmental exposure estimation of the substance, as requested by ECHA.

### 7.12.1. Human health

#### 7.12.1.1. Worker

The level of exposure is considered acceptable.

#### 7.12.1.2. Consumer

The level of exposure is considered acceptable.

### 7.12.2. Environment

#### 7.12.2.1. Aquatic compartment (incl. sediment)

The level of exposure is considered acceptable except for uses argued below (see section 7.13).

#### 7.12.2.2. Terrestrial compartment

The level of exposure is considered acceptable.

#### 7.12.2.3. Atmospheric compartment

n/a

### 7.12.3. Combined exposure assessment

The level of exposure is considered acceptable except for uses argued below (see section 7.13).

## 7.13. Risk characterisation

Human

The CSRs were updated taking into account the potential combined exposure for workers and when appropriate the RMMs were refined. Aggregated RCRs for workers and consumers resulted in values below 1, indicating that combined exposure for systemic long term effects can be regarded as safe for all exposure scenarios.

Environment

Aquatic compartment (incl. sediment)

The eMSCA concludes that for the following scenarios the derived RCRs for freshwater, sediment (freshwater), marine water and sediment (marine water) are below 1, but close to it:

- ES3 "Formulation of hydroquinone for photographic processing (liquid)";
- ES7 "Use in photographic processing (Photographic industry)";
- ES8 "Use as process additive - inhibitor I (polymerization prevention, continuous process)";
- ES9 "Use as process additive - inhibitor II (polymerization prevention, batch process)";

Terrestrial compartment

All the RCR values are below 1

Overall risk characterization

All the RCR values are below 1

Environment (combined for all exposure routes)
The eMSCA concludes that for the following combined uses at site the derived RCRs for freshwater, sediment (freshwater), marine water and sediment (marine water) are below 1, but close to it:
ES2 "Formulation of hydroquinone for photographic processing (solid)"and ES3 "Formulation of hydroquinone for photographic processing (liquid)".

## 7.14. References

Registration dossier for Hydroquinone, European Chemicals Agency.
http://echa.europa.eu/

## 7.15. Abbreviations

AF Assessment factor
BW Body weight
CAS Chemical abstracts service
C&L Classification and labelling
CLP Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR Carcinogenicity, mutagenicity and toxicity to reproduction
DMEL Derived Minimal Effect Level
DNEL Derived no effect level
ES Exposure Scenario
eMSCA Evaluating Member State Competent Authority
NOAEC No Observed Adverse Effect Concentration
NOAEL No Observed Adverse Effect Level
OECD Organisation for Economic Co-operation and Development
PBT Persistent, Bioaccumulative, Toxic
PEC Predicted Environmental Concentration
PNEC Predicted No Effect Concentration
RCR Risk characterization ratio
RMMs Risk Management Measures
vPvB Very Persistent and very Bioaccumulative