BUREAU FOR CHEMICAL SUBSTANCES

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

4-tert-butylpyrocatechol

EC No 202-653-9

CAS No 98-29-3

Evaluating Member State(s): Bureau for Chemical Substances, Poland

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2018

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

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

4-Tert-butylpyrocatechol (4-TBC) was originally selected for substance evaluation in order to clarify concerns about:

- suspected Mutagenic – this endpoint was not evaluated due to the ECHA decision requesting a Comet assay by 29 November 2021,

- suspected endocrine disruptor (ED),

- suspected skin sensitiser,

- suspected PBT/vPvB,

- exposure of workers,

- exposure of environment.

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

- skin corrosion,
- serious damage to eyes.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Three dossier evaluation decisions have been issued by ECHA:

https://echa.europa.eu/documents/10162/64c8367c-ccf4-087e-5325-73a27ed23d5d

https://echa.europa.eu/documents/10162/e8dba27a-c439-39bb-15a9-fb4fa1b7d397

https://echa.europa.eu/documents/10162/dbe1f867-4354-09b9-fed7-c9e0bf712483

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	
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	

Some of the initial and additional concerns were removed based on the data submitted in the updated registration dossier and in the publicly available literature.

After finalising the substance evaluation, the Polish Competent Authority (eMSCA) concluded that 4-TBC is not persistent, not bioaccumulative and not toxic. Consequently, the evaluating MSCA overall concludes that 4-TBC is not PBT/vPvB. The initial concern for endocrine disruption was not confirmed for 4-TBC based on the assessment of the currently available information. However, it is noted that an OECD 443 study has been requested in an ECHA decision and this may bring further information relevant for the assessment of endocrine disruption properties when the results are available.

Self-classification of 4-TBC in the updated registration dossier as Skin Sens. 1A, Skin Corr. 1 B and Eye Dam. 1 is considered by the eMSCA to be appropriate.

Regarding the exposure concern, the use information and the exposure data provided in the registration dossier suggested no risk for the workers and environment. However, we recommend revision of the exposure assessment for workers, as explained in Section 7.12.1.1.

These conclusions were based on the originally available and updated registration dossiers and information from registrants, as well as the publicly available literature.

The available information is sufficient and reliable to clarify the initial concerns. The mutagenic concern has not been clarified, but a study was requested under dossier evaluation.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

4-TBC currently has no harmonised classification in accordance with Regulation (EC) 1272/2008. The classification proposed below is based on currently available information. A further follow-up action cannot be excluded when new information resulting from the testing proposal decision (see Section 7.2) becomes available.

Table 2: Classification and labelling proposal of 4-TBC

Classification and Labelling	Pictograms, Signal word
Acute Tox. 4 H302: Harmful if swallowed.	GHS05: corrosion GHS07: exclamation mark GHS09: environment
Acute Tox. 4 H312: Harmful in contact with skin	
Skin Corr. 1 B H314: Causes severe skin burns and eye damage.	
Eye Dam. 1 H318: Causes serious eye damage	
Skin Sens. 1A H317: May cause an allergic skin reaction	
Aquatic Acute 1 H400: Very toxic to aquatic life. M=1	
Aquatic Chronic 1 H410: Very toxic to aquatic life with long lasting effects. M=1	

The outcomes of the evaluation performed by eMSCA lead to conclusion that a new entry in CLP-Annex VI for 4-TBC should be proposed.

Acute Oral toxicity

Based on the key study with reliability 1 submitted in the registration dossier (unpublished study, 1992), the oral LD_{50} was calculated as 815 mg/kg b.w. Therefore, based on this value, 4-TBC required classification as Acute Tox. 4, H302: Harmful if swallowed (Acute Tox. 4, H302), according to the CLP Regulation/UN GHS.

Acute Dermal toxicity

Based on the key study with reliability 1 submitted in the registration dossier (unpublished study, 1992), the dermal LD_{50} was calculated as 1331 mg/kg b.w. Therefore, based on this value, TBC required classification as Acute Tox. 4, H312: Harmful in contact with skin (Acute Tox. 4, H312), according to the CLP Regulation/UN GHS.

Skin corrosion/irritation

The results of available studies support classification of 4-TBC as corrosive category 1, H314 (unpublished studies, 1987 and 1993).

Serious eye damage/eye irritation

Studies on eye irritation performed with rabbits and available for evaluator confirm properties of the substance as inducing irreversible effects on eyes (unpublished studies, 1987 and 1996).

Skin sensitisation

Based on reliable and GLP-compliant LLNA study (unpublished study, 2003) strong potency to cause skin sensitisation by 4-TBC can be confirmed. Thus, the substance should be classified as Skin Sens. 1A, H317 (the reported LLNA study shows a Stimulation Index ≥3 at all tested concentrations (1%, 2.5%, 5%), therefore EC3 value ≤2% was obtained).

Germ cell mutagenicity

There is one equivocal (IP, rat) and one negative (oral, mouse) micronucleus test (MN). The in vitro studies contain a positive mouse lymphoma TK assay (MLA) but otherwise negative results. Thus, there may be concern, but the data is currently not sufficient to conclude on potential mutagenicity. However, an in vivo mammalian alkaline comet assay has been requested by November 2021 in a testing proposal decision from ECHA. Therefore no further information needs to be requested under this substance evaluation.

Conclusion on environmental classification

Based on acute toxicity tests on fish (unpublished study, 2010) and test on aquatic invertebrates (unpublished study, 2010), 4-TBC appears to be very toxic to aquatic organisms with reliable L/EC_{50} values < 1 mg/L. As a consequence, 4-TBC warrants classification as Aquatic Acute 1 (H400) with an M factor = 1 under Regulation (EC) No 1272/2008.

A chronic Daphnia magna study is also available and it resulted in a NOEC (21-days) of 0.135 mg/l (unpublished study, 2013). Based on this chronic data and the conclusion that

4-TBC is not rapidly degradable, the substance warrants classification as Aquatic Chronic Category 2 (H411) under Regulation No. 1272/2008 (Annex 1 of CLP Regulation, Table 4.1.0 (b)(i): 0,1 mg/l < NOEC ≤ 0,1 mg/l). However, as no chronic data is available for fish, figure 4.1.1 requires that the available acute toxicity data for fish is compared with the criteria in table 4.1.0(b)(iii). As 4-TBC is not rapidly degradable and has an LC_{50} < 1 mg/L, classification as Aquatic Chronic 1 is warranted. As chronic 1 is the outcome, comparing the data with the acute toxicity criteria of table 4.1.3 results in an M-factor of 1. As this surrogate approach indicates a more stringent classification outcome than that derived by using chronic data, this more stringent outcome is used for classification.

In conclusion, 4-TBC appears to warrant classification as Aquatic Acute 1 (H400), M=1 and Aquatic Chronic 1 (H410), M=1.

4.1.2. Restriction

Not applicable.

4.1.3. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Not applicable.

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

Table 4

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLP Annex VI proposal	To be decided*	Poland

*The eMSCA considers that CLH is required and is a priority for Aquatic Chronic. Before submitting a CLH proposal, eMSCA Poland will wait for the outcome of the ongoing studies on reproductive toxicity and mutagenicity.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

4-TBC was originally selected for substance evaluation in order to clarify concerns about:

- suspected Mutagenic – not evaluated due to the ECHA decision requesting a Comet assay by 29 November 2021,
- suspected endocrine disruptor (ED),
- suspected skin sensitiser,
- suspected PBT/vPvB,
- exposure of workers,
- exposure of environment.

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

- skin corrosion
- serious damage to eyes

Table 5

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Suspected Mutagenic	not evaluated due to the ECHA decision requesting a Comet assay by 29 November 2021
Suspected ED	Not confirmed
Suspected skin sensitiser	Confirmed
Suspected PBT/vPvB	Not confirmed
Exposure of workers	Refinement of worker exposure assessment is recommended
Exposure of environment	Not confirmed

7.2. Procedure

The updated Community rolling action plan (CoRAP) was published on the ECHA website on 20 March 2018.

The substance evaluation was performed based on the updated registration dossier and Chemical Safety Reports (CSRs) as well as on the basis of additional information available in scientific databases and publications.

All the information was assessed regarding reliability for evaluation of the main grounds of concern. The particular emphasis was placed on the possible PBT/vPvB and ED properties of 4-TBC. Other aspects as physical and chemical properties have been checked and described in general in this report.

The results of the evaluation are documented in this report. Available information is enough to clarify the initial concerns. Thus, no further information is requested under this substance evaluation.

In testing proposal decision TPE-D-2114449853-39-01/F dated 21 November 2018, the registrant(s) of 4-TBC with tonnage band of 1000 tonnes or more per year were requested to provide an in vivo mammalian alkaline comet assay and an extended one-generation reproductive toxicity study by 29 November 2021.

7.3. Identity of the substance

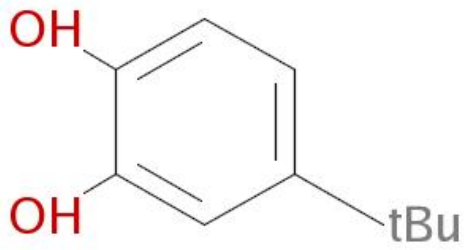
The substance 4-TBC is a mono constituent substance (origin: organic) having the following characteristics and physical–chemical properties.

Table 6

SUBSTANCE IDENTITY	
Public name:	4-TBC
EC number:	202-653-9
CAS number:	98-29-3
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C10H14O2
Molecular weight range:	166.217
Synonyms:	1,2-Benzenediol, 4-(1,1-dimethylethyl)- 4-tert-butylbenzene-1,2-diol

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

Structural formula:



7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	solid
Vapour pressure	0.103 Pa at 30°C to 1.095 Pa at 50°C (transpiration method)
Water solubility	4.2 g/L +/- 0.5 g/L at 20°C (OECD Guideline 105)
Partition coefficient n-octanol/water (Log Kow)	1.98 at the temperature of 25 °C (flask method)
Flammability	4-TBC is non flammable when tested according to A10 method
Explosive properties	4-TBC does not present a danger of explosion (EU Method A.14)
Oxidising properties	study not needed
Granulometry	1000 to 5000 µm (sieving analysis)
Stability in organic solvents and identity of relevant degradation products	the study does not need to be conducted - the stability of the substance is not considered to be critical
Dissociation constant	9.53 (for hydroxyl in position 2) and 14.0 (for hydroxyl in position 1) at 20°C
Melting / freezing point	54.95°C +/- 0.05°C (thermal analysis)
Boiling point	290.5°C +/- 0.1°C (differential scanning calorimetry)
Relative density	1.085 +/- 0.012 at 20°C (pycnometer method)
Flash point range	157 - 159°C at 1005 hPa (closed cup)
Self-ignition temperature	435°C at 996 - 1000 hPa (EU Method A.15)

7.5. Manufacture and uses

7.5.1. Quantities

This substance has 8 active registrations under REACH (1 joint submission).

Table 8

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

7.5.2. Overview of uses

Table 9

REGISTERED USES	Use(s)
Uses as intermediate	uses as intermediate
Formulation	formulation of mixtures
Uses at industrial sites	used in the following products: polymers, coating products and fillers, putties, plasters, modelling clay used for the manufacture of: chemicals and plastic products. thermoplastic manufacture and use as processing.
Uses by professional workers	ECHA has no public registered data indicating whether or in which chemical products the substance might be used.
Consumer Uses	-
Article service life	-

4-TBC is used as a stabilizer and an inhibitor of polymerization processes.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

4-TBC (CAS No. 98-29-3) is not included in the Annex VI of CLP Regulation.

7.6.2. Self-classification

In the registration(s):

Table 10 Registered classification

Hazard Class and Category Codes	Hazard Statement Codes

Acute Tox. 4	H302
Acute Tox. 4	H312
Skin Corr. 1	H314
Eye Dam. 1	H318
Skin Sens. 1A	H317
Aquatic Acute 1, M=1	H400
Aquatic Chronic 2	H411

The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory (2019-10-15)*:*

The notified classification for 4-TBC is given in the table 11.

Table 11 The notified classification

Hazard Class and Category Codes	Hazard Statement Codes
Acute Tox. 4	H302
Acute Tox. 3	H311
Acute Tox. 4	H312
Skin Corr. 1A	H314
Skin Corr. 1B	H314
Skin Corr. 1C	H314
Skin Irrit. 2	H315
Eye Dam. 1	H318
Eye Irrit. 2	H319
Skin Sens. 1	H317
Carc. 2	H351 (dermal)
Repr. 2	H361 (dermal)
STOT SE 3	H335
Aquatic Acute 1, M=1	H400
Aquatic Chronic 1, M=1	H410
Aquatic Chronic 2	H411

7.7. Environmental fate properties

7.7.1. Degradation

Hydrolysis

The hydrolysis preliminary test of 4-TBC conducted according to OECD guideline n°111 (Hydrolysis as a Function of pH)/ EU Method C.7 (Degradation: Abiotic Degradation: Hydrolysis as a Function of pH) was available. The study showed that the substance was stable at pH 4.0 and 50°C but degraded at pH 7.0 and 9.0 at 50°C.

The degradation of the test item at pH 7.0 and pH 9.0 may not be caused by hydrolysis but oxidation reactions. It is well-known in the specific literature that catechols can be oxidized to quinones.

Additionally, the substance is an alkyl-substituted phenol derivative and has no functional groups that can be hydrolysed. Therefore from the structure of the substance it can be deduced that it does not undergo abiotic degradation through hydrolysis.

In conclusion hydrolysis is not considered a relevant degradation mechanism for 4-TBC.

Biodegradation

Estimated data

The eMSCA used BIOWIN QSAR models (QSAR Toolbox 4.2) for the estimation of biodegradability of 4-TBC.

The results of the individual BIOWIN models for 4-TBC, are presented in Table 14.

Table 12 Biowin results

4-TBC		
Model	**Probability**	**Prediction**
Biodeg probability (Biowin 1)	0,7161	biodegrades fast >0.5
Biodeg probability (Biowin 2)	0,6775	biodegrades fast >0.5
Ultimate biodegradation time (Biowin 3)	2,7325	biodegrades fast > 2.25
Biodeg probability (Biowin 5)	0,4396	Does NOT Biodegrade Fast <0.500
Biodeg probability (Biowin 6)	0,3826	Does NOT Biodegrade Fast <0.500
Biodeg probability (Biowin 7)	0,1383	Does NOT Biodegrade Fast <0.500
Custom QSAR model - Example Prioritization Scheme (PBT)	-	P*

*QSAR Toolbox 4.2 system collects persistent (P) experimental data in the Toolbox databases and applies BIOWIN 5 and BIOWIN 6 models.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.11, table R.11-4, a substance is potentially P or vP if the Biowin 6 prediction is <0.5 and the Biowin 3 prediction <2.25 to 2.75. For 4-TBC, this condition is met for its Biowin 3 and Biowin 6 predictions. For a Biowin 3 prediction between 2.25 and 2.75, more degradation relevant information is generally warranted. QSAR data could not be used to conclude on persistency of this substance.

Measured data

In the registration dossier two screening tests for biodegradation in water were submitted on 4-TBC, i.e. inherent biodegradability test (OECD 302B; registration dossier, study 2009) and ready biodegradability test (similar to OECD 310; registration dossier, study 2002).

Inherent biodegradability test according to OECD 302B.

4-TBC was investigated for its potential (inherent) ultimate biodegradability in a Zahn-Wellens / EMPA test over 28 days. The inoculum was activated sludge taken from a sewage treatment plant treating domestic wastewater and was not adapted.

The test is considered as valid, since the following criteria of OECD 302 B and EU method C.9 are fulfilled:

- the DOC of the reference item diethylene glycol in the procedure control is removed by at least 70% within 14 days of exposure, thus confirming suitability of the activated sludge.
- DOC removal in the test item flasks took place relatively gradually
- no DOC removal for the test item within the first 3 hours of exposure which is an indication that the test item did not adsorb on activated sludge.

In the toxicity control, containing the test item, the reference item diethylene glycol and activated sludge (inoculum) the initial DOC decreased by 81% within 14 days of exposure. Thus, according to the test guidelines the test item was not inhibitory to activated sludge at the tested concentration of 143.5 mg/L because degradation was >35% within 14 days. To conclude, more than 70% degradation of the test item (4-TBC) occurred within the first seven days of the test, including the lag-phase and the log-phase. The log-phase was lower than 3 days.
Therefore, 4-TBC could be considered as inherent ultimately biodegradable according to OECD (2006)[2].

Ready biodegradability

The second available test, i.e. Headspace Test (Ready Biodegradability – CO_2 in sealed vessels; TG 310) for ready biodegradability, represents an alternative to the CO_2 Evolution Test (TG 301 B). In this test the CO_2 evolution resulting from the ultimate aerobic biodegradation of the test substance is determined by measuring the inorganic carbon (IC) produced in sealed test bottles, and the pass level has been defined as 60% of theoretical maximum IC production (ThIC).

The test was designed to be compatible with the guideline ISO 14593. It means that the test procedure was equivalent or similar to OECD Guidance 310 (Ready Biodegradability - CO_2 in Sealed Vessels). The test was performed in noncompliance with GLP standards. It was conducted in sealed vessels.

[2] OECD (2006) : Revised introduction to the OECD guidelines for testing of chemicals, section 3 – Part 1

The test report concluded that 4-TBC attained 24.7% degradation after 28 days and therefore cannot be considered as readily biodegradable.

Summary and discussion on degradation

Hydrolysis is not considered a relevant degradation mechanism for 4-TBC. Based on the structure of the substance it can be deduced that it does not undergo abiotic degradation through hydrolysis.

With reference to biodegradability, there are two tests available, one on ready biodegradability and another on inherent biodegradability. In spite of some deficiencies in ready biodegradability test the 24.7% degradation of 4-TBC after 28 days was observed. Therefore on the basis of this study, substance cannot be considered as readily biodegradable. However, according to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.11, Section R.11.4.1.1.3 (version 3.0, June 2017) a negative result of the screening tests on ready biodegradability does not necessarily mean that the substance will not be degraded relatively fast under environmental conditions. The inherent biodegradability test indicates that more than 70% degradation of the test item (4-TBC) occurred within the first seven days of the test, including the lag-phase and the log-phase. The log-phase was lower than 3 days. Therefore, 4-TBC could be considered as inherent ultimately biodegradable.

Inherent biodegradability data may be used directly for the assessment of environmental persistence of the substance as specified in guidance "Chapter R.7b: Endpoint specific guidance" section R.7.9.5.2 and Chapter R.11: PBT/vPvB assessment of the Guidance on IR&CSA).
Based on the available data, the eMSCA concludes that 4-TBC should be regarded as biodegradable in water, sediment, and soil in the context of environmental assessment under REACH.

7.7.2. Environmental distribution

In the registration dossier two tests on adsorption of 4-TBC were submitted, i.e. test on Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)) (OECD Guideline 121; registration dossier, study 2010) and test on the adsorption of 4-TBC by soil clay minerals (no guideline available; registration dossier, study 1965).

In the first study the log Koc of 4-TBC in soil was found to be 1.374. Therefore, 4-TBC is considered as highly mobile in soils.

The second study (supporting study with reliability 2) investigated the possible adsorption of 4-TBC on various clay minerals. The adsorption of 4-TBC by clay minerals is initially quite rapid, and then continue for an extended period of time at a relatively slow rate. The adsorption of 4-TBC by clay from water is quite strong.

The generic Mackay level III fugacity model was used to obtain the potential environmental distributions of 4-TBC. The results show that, if 4-TBC is released into water, it is unlikely to be distributed into other compartments. If it is released into air and soil, it is likely to be distributed to water or soil.

4-TBC is not considered as persistent or very persistent substance. The log Koc for 4-TBC is below 4, indicating that the mobility criterion is fulfilled.

In conclusion the PMT criteria presented in the background document for the workshop:

"PMT and vPvM substances under REACH"[3]. are not fulfilled based on the currently available data.

7.7.3. Bioaccumulation

No bioaccumulation data are available in the registration dossier for the 4-TBC.

The bioaccumulation potential for aquatic organisms was assessed based on the screening criteria - experimental data on n-octanol/water partition coefficient.

Determination of the n-octanol/water partition coefficient of 4-TBC was performed according to OECD 107 (Shake Flask Method) and EU Method A.8. This study (unpublished study, 2010), with reliability 1 according to Klimisch, was selected as a key study. The average n-octanol/water partition coefficient (Kow) of 4-TBC is 103.66. The decimal logarithm of n-octanol/water partition coefficient (Log Kow) is 1.98.

An additional experimental data (log Kow = 2.94) coming from peer-review handbooks, were available in the registration dossier. However there was no information about test guideline and this result can be consider only as supporting information.

The predicted log Kow (KOWWIN) estimated by eMSCA for the 4-TBC - Log Kow = 2.94.

Bioaccumulation estimated by eMSCA by BCFBAF v3.01:
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt).

For the organic substances with a log Kow value below 4.5 it is assumed that the affinity for the lipids of an organism is insufficient to exceed the B criterion (BCF > 2000).

The log Kow at 1.98 for 4-TBC is lower than the screening criterion 4.5 and based on this data it can be considered that 4-TBC has a low potential for bioaccumulation in aquatic organisms.

The bioaccumulation potential for air-breathing organisms was assessed based on the screening criteria – experimental data on n-octanol/water partition coefficient and estimated n-octanol/air partition coefficient.

The predicted log Koa (EpiSuite) estimated by eMSCA for the 4-TBC – log Koa = 10.2

The log Kow at 1.98 is lower than the screening criterion 2 and the log Koa at 10.2 is above the screening criterion 5. Since logKow value coming from reliable experimental study is lower than 2 therefore TBC-4 is not considered as potentially bioaccumulative in air breathing organisms based on screening criterion.

There are no relevant data available in the registration dossier and literature regarding bioaccumulation of 4-TBC in terrestrial organisms.

However, the absorption, distribution, metabolism, and excretion of 4-TBC were determined in rats and mice. 4-TBC was readily absorbed following oral and dermal administration. Metabolism led to conjugation and methylation products. 4-TBC was excreted as 4-tert-butylpyrocatechol sulfate and other polar metabolites. Based on the results of these studies, 4-TBC was not expected to bioaccumulate.

Summary and discussion of bioaccumulation

The log Pow at 1.98 for 4-TBC is lower than the screening criterion 4.5 and based on this data it can be considered that 4 -tert-butylpyrocatechol has a low potential for

[3] Workshop on "PMT and vPvM substances under REACH", March 13'th-14'th, Bundespresseamt, Berlin, Germany, *Preliminary assessment of substances registered under REACH that could fulfil the proposed PMT/vPvM criteria,* (NGI, 2018)

bioaccumulation in aquatic organisms

Since logKow value coming from reliable experimental study is lower than 2 therefore TBC-4 is not considered as potentially bioaccumulative in air breathing organisms based on screening criterion. The results of toxicokinetic studies show that 4-TBC was not expected to bioaccumulate.

On the basis of the available information, the eMSCA considers the 4-TBC as not potentially bioaccumulative.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Short-term toxicity to fish

Method	Results	Remarks	Reference
Danio rerio Freshwater semi-static short-term toxicity to fish according to OECD Guideline 203 (Fish, Acute Toxicity Test); according to EU Method C.1 (Acute Toxicity for Fish)	96h LC50= 0.12 mg/L test mat. (meas. (geom. mean)) based on: mortality 96h NOEC=0.16 mg/L test mat. (meas. (geom. mean)) based on: mortality	1 (reliable without restriction) GLP	Registration dossier (study report, 2010)

Long-term toxicity to fish

No relevant information available.

7.8.1.2. Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna Freshwater semi-static according to OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test); according to EU Method C.2 (Acute Toxicity for Daphnia)	EC50 (24h): 0.94 mg/L test mat. (meas. (geom. mean)) EC50 (48h): 0.48 mg/L test mat. (meas. (geom. mean)) EC100 (48h): 1.97 mg/L test mat. (meas. (geom. mean)) NOEC (48h): <0.18 mg/L test mat. (meas. (geom. mean))	1 (reliable without restriction) key study experimental study **Test material** 4-tert-butylbenzene-1,2-diol / 98-29-3 / 202-653-9	Registration dossier (study report, 2010)
Daphnia magna Static according to EU Method C.2	EC50 (24h): 1.9 mg/L test mat. (nominal) EC50 (48h): 1.4 mg/L test mat. (nominal)	3 (not reliable) disregarded due to major methodological deficiencies	Registration dossier (study report, 1995)

(Acute Toxicity for Daphnia)		experimental study **Test material** 4-tert-butylbenzene-1,2-diol / 98-29-3 / 202-653-9,	

Long-term toxicity to aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater long-term toxicity to aquatic invertebrates according to OECD Guideline 211 (Daphnia magna Reproduction Test) ; according to EU Method C.20 (Daphnia magna Reproduction Test)	NOEC (21d): 135 µg/L test mat. (meas. (geom. mean)) LOEC (21d): 359 µg/L test mat. (meas. (geom. mean)) EC50 (21d): >359 µg/L test mat. (meas. (geom. mean)) EC50 (21d): >359 µg/L test mat. (meas. (geom. mean))	1 (reliable without restriction) key study experimental study **Test material** 4-tert-butylbenzene-1,2-diol / 98-29-3 / 202-653-9, Form: solid: flakes	Registration dossier (study report, 2013)

7.8.1.3. Algae and aquatic plants

Method	Results	Remarks	Reference
Pseudokirchneriella subcapitata (previous names: Raphidocelis subcapitata, Selenastrum capricornutum) Freshwater toxicity to aquatic algae and cyanobacteria according to OECD Guideline 201 (Alga, Growth Inhibition Test) [before 23 March 2006] ; according to EU Method C.3 (Algal Inhibition test)	EC50 (72h): 10.17 mg/L test mat. (meas. (geom. mean)) NOEC (72h): 0.2 mg/L test mat. (meas. (geom. mean)) LOEC (72h): 0.46 mg/L test mat. (meas. (geom. mean)) EC10 (72h): 2.29 mg/L test mat. (meas. (geom. mean)) EC20 (72h): 3.82 mg/L test mat. (meas. (geom. mean))	1 (reliable without restriction) key study experimental study **Test material** 4-tert-butylbenzene-1,2-diol / 98-29-3 / 202-653-9, Form: solid: flakes	Registration dossier (study report, 2010)

7.8.1.4. Sediment organisms

No relevant information available.

7.8.1.5. Other aquatic organisms

No relevant information available.

7.8.2. Terrestrial compartment

No relevant information available.

7.8.3. Microbiological activity in sewage treatment systems

Toxicity to aquatic micro-organisms

Method	Results	Remarks	
OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test	NOEC (3h): 0.6 mg/L test mat. (nominal) EC50 (3h): 16 mg/L test mat. (nominal)	1 (reliable without restriction) key study experimental study **Test material** 4-tert-butylbenzene-1,2-diol / 98-29-3 / 202-653-9	Registration dossier (study report, 2009)

7.8.4. PNEC derivation and other hazard conclusions

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 1.2µg/L Intermittent releases: 1.2µg/L	Assessment factor: 100 Extrapolation method: assessment factor
Marine water	PNEC aqua (marine water): 0.12µg/L	Assessment factor: 1000 Extrapolation method: assessment factor The reasoning is the same as for PNEC aqua (freshwater) except that an assessment factor of 1000 is applied instead of 100.
Sediments (freshwater)	PNEC sediment (freshwater): 6.9µg/kg sediment dw	Assessment factor: Extrapolation method: equilibrium partitioning method
Sediments (marine water)	PNEC sediment (marine water): 0.69µg/kg sediment dw	Assessment factor: Extrapolation method: equilibrium partitioning method
Sewage treatment plant	PNEC STP: 0.16mg/L	Assessment factor: 100 Extrapolation method: assessment factor
Soil	PNEC soil: 0.68µg/kg soil dw	Assessment factor: Extrapolation method: equilibrium partitioning method
Air	no hazard identified:	No data is available.

Secondary poisoning	no potential for bioaccumulation	No study on bioaccumulation is available. However, the measured log kow value is 1.98 (unpublished study, 2009). As a consequence, 4-TBC is considered to have a low potential for bioaccumulation, and no PNEC oral was calculated.

7.8.5. Conclusions for classification and labelling

Table 25 The proposal for harmonised classification

Hazard Class and Category Codes	Hazard Statement Codes
Aquatic Acute 1	H400 M=1
Aquatic Chronic 1	H410 M=1

Justification of environmental classification:

Biodegradability in water

Ready biodegradability:

All organic substances that degrade to a level higher than the pass level in a standard OECD ready biodegradability test or in a similar test should be considered readily biodegradable, and consequently also rapidly degradable.

In the key study, the biodegradation of 4-TBC was followed during 28 days according to OECD guideline 310, at an initial concentration of 20 mg carbon/L (27.7 mg 4-TBC/L). Inoculum used in the test was an activated sludge at a concentration of 4 mg/L taking in an aeration basin of a sewage treatment plant of domestic effluents. After 28 days, the percentage of degradation was 24.7% based on CO_2 evolution. On the basis of this study, 4-TBC is not readily biodegradable.

Inherent biodegradability:

The inherent biodegradability of 4-TBC (initial concentration: 143 mg/L), was tested in a Zahn-Wellens test during 28 days according to OECD guideline 302B. Inoculum used in a study was 300 mg/L of a sludge from a wastewater treatment plant, non-adapted. After 28 days, the corresponding percentage of biodegradation obtained was 91% of DOC removal. More than 70% degradation of 4-TBC occurred within the first seven days of the test, including the lag-phase and the log-phase. The log-phase was lower than 3 days. Under the test conditions, 4-TBC is considered as inherent ultimately biodegradable.

According to Point II.2.3.4 (Inherent and Enhanced Ready Biodegradability tests) of Annex II) of Guidance on the Application of the CLP Criteria Version 5.0 – July 2017 "Substances that are degraded more than 70% in tests for inherent biodegradability (OECD Test Guidelines 302) have the potential for ultimate biodegradation. However, because of the optimised conditions in these tests, the rapid biodegradability of inherently biodegradable substances in the environment cannot be assumed. The optimised conditions in inherent biodegradability tests stimulate adaptation of the micro-organisms thus increasing the

biodegradation potential, compared to natural environments. Therefore, positive results in general should not be interpreted as evidence for rapid degradation in the environment."

General conclusion: Based on the available information relevant for classification, 4-TBC is "not readily biodegradable" according to the results of key study, OECD 310) and is therefore considered as not rapidly degradable for the purposes of classification.

Aquatic acute and aquatic chronic classification:

Based on acute toxicity tests on fish (LC_{50} (96 hours) = 0.12 mg/L and on invertebrates (EC_{50} (48 hours) = 0.48 mg/L), 4-TBC appears to be very toxic to the aquatic organisms, with reliable L/EC_{50} values < 1 mg/L. As a consequence, 4-TBC warrants classification as Aquatic Acute 1 (H400) with an M-factor = 1, under Regulation (EC) No 1272/2008.

A chronic Daphnia magna study, which is also available, resulted in a NOEC (21-days) of 0.135 mg/l. Based on this chronic data and the conclusion that 4-TBC is not rapidly degradable, the substance warrants classified as Aquatic Chronic Category 2 (H411) under Regulation No. 1272/2008 (Annex 1 of CLP Regulation, Table 4.1.0 b) (i): 0,1 mg/l < NOEC ≤ 0,1 mg/l.). However, as no chronic data is available for fish, figure 4.1.1 requires that the available acute toxicity data for fish is compared with the criteria in table 4.1.0(b)(iii). As 4-TBC is not rapidly degradable and has an LC50 < 1 mg/L, classification as Aquatic Chronic 1 is warranted. As chronic 1 is the outcome, comparing the data with the acute toxicity criteria of table 4.1.3 results in an M-factor of 1. As this surrogate approach indicates a more stringent classification outcome than that derived by using chronic data, this more stringent outcome is used for classification.

In conclusion, 4-TBC appears to warrant classification as Aquatic Acute 1 (H400), M=1 and Aquatic Chronic 1 (H410), M=1.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The absorption, distribution, metabolism, and excretion of 4-TBC following intravenous injection, gavage dosing or dermal application were determined in rats and mice. 4-TBC was readily absorbed following oral and dermal administration. It is not expected to bioaccumulate. Metabolism led to conjugation and methylation products. 4-TBC was excreted as 4-tert-butylpyrocatechol sulfate and other polar metabolites. There was no evidence in the metabolites for the formation of reactive intermediates (NTP 2002, Registration Dossier 2017).

7.9.2. Acute toxicity and Corrosion/Irritation

The relevant information on the acute toxicity was submitted by the registrant. In the CSR more studies are presented but some of them is disregarded due to the methodological deficiencies.

Acute oral

Three acute oral toxicity tests were evaluated. One of them is a key study with reliability of 1 according to Klimisch criteria. Two others are supporting studies with reliability 2, however in the opinion of eMSCA one of them should be disregarded because of the lack of information on the exposure, course of the experiment and its results. The LD50 value was established based on the key study whose results are described below.

In the key study the mortality in males was 0%, 20%, 60%, 100%, and 100% at the dose levels of 490, 680, 880, 1200 and 2000 mg/kg respectively. The mortality in the females was 0%, 60% and 100% at 680, 880 and 2000 mg/kg respectively. The necropsy of animals

found dead showed signs of ulceration of the stomach at all dose levels. The macroscopic observation revealed no abnormalities in the animals sacrificed at the end of the study. The observed decrease in body weight gain, sometimes resulting in body weight loss, in few surviving animals returned to normal after day 5. It can be stated that, according to the results, the LD50 in the females was similar to that of males - 815 mg/kg bw.

Acute dermal

Two acute dermal toxicity tests were evaluated. One of them is a key study with reliability of 1 according to Klimisch criteria. The second one is supporting study with reliability 2. The LD50 value was established based on the key study which results are described below.

In the key study the mortality in males was 0%, 0%, 60% and 40% at the dose levels of 500, 750, 1120 and 1690 mg/kg respectively. The mortality in females was 40% and 60% at the dose levels of 750 and 1120 mg/kg respectively. During the first few hours following application of the test substance, hypokinesia, sedation and dyspnoea were noted in all treated animals. Clinical signs had reversed by day 3 at 500 mg/kg, by day 5 at 750 mg/kg and by day 7 at 1120 and 1690 mg/kg. After the removal of the dressing and for at least one week, signs of severe cutaneous reactions were observed at all dose levels.

It can be stated that, according to these results, the dermal LD50 in the females was similar to that of males - 1331 mg/kg bw.

Acute Inhalation toxicity

No data is available for this route of administration.

Likely route of human exposure is more in favor of acute dermal toxicity study than inhalation one

Skin irritation/corrosion

Four available dermal irritation studies available in the registration dossier were evaluated. In the first one New-Zealand White rabbits (6 males) were dermally exposed to 0.5 mL of 4-TBC 85% in water on a 6 cm2 body surface area. Test sites were covered with a semi-occlusive dressing for 4 hours. Animals were then observed for 14 days. Irritation was scored by the method of TG OECD 404.

After 1 hour of exposure, severe erythema and moderate or severe oedema were observed in all treated animals. Severe erythema was not reversible after 14 days and oedema was fully reversible within 14 days. The study report does not contain description of nature and degree of irritation or corrosion observed, and any histopathological findings. There was only limited description of irreversible lesions: 'aspect of burn on all the zone of application' and 'presence of eschars on all the zone of application for all animals, 14 days after exposure'. Therefore, these findings could not be identified as irritation or corrosion. In the second one three New Zealand White rabbits were dermally exposed to 0.5 g of 4-TBC on 2.5 cm² body surface area. Test sites were covered with a semi-occlusive dressing for three minutes. Animals were then observed for 14 days. Irritation was scored by the method of guideline OECD n°404.

Necrosis with slight oedema was evident at all three treatment sites following the three-minute exposure period. These reactions persisted and were still visible at two sites on day 14. No information on corrosive responses during an observation period ≤ 1 h after exposure were provided. However, the study results are sufficient for classification of 4-TBC as corrosive substance category 1 without sub-categorisation since criterion of classification in category 1 is met (visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure ≤ 4 h).

The *in vivo* test in rabbits according to OECD TG 404 is the standard in vivo test for the hazard assessment under REACH. The study results submitted by the registrant are accepted by the eMSCA.

4-TBC produced severe erythema which was irreversible within 14 days of the observation and severe/moderate or slight oedema which was reversible in the first study. In the second one erythma was accompanying with the visible necrosis.

The other two studies, performed respectively on the guinea pig and rabbits, confirm the skin corrosive/irritating potential of 4-TBC.

In the opinion of eMSCA, 4-TBC fulfils CLP classification criteria as a corrosive substance category 1.

Eye irritation/corrosion

Two studies on eye irritation are available. In the first one, 0.1 mL 4 -tert-butylpyrocatechol 85% in water was instilled into the conjunctival sac of the right eye of hybrid Albino New-Zealand White rabbits (6 males - no rinsing). Animals were then observed for 21 days. Ocular irritation was scored by the method of directive OECD 405.

After 1 hour of exposure, severe corneal opacity and iris lesions, moderate (4/6 rabbits) or severe (2/6 rabbits) chemosis and slight conjunctival redness were observed in all treated animals. These ocular irritation signs were not reversible after 21 days. In this study, 4 -tert-butylpyrocatechol 85% in water was highly irritating to the eye or causing irreversible effects on the eye based on the observed ocular reactions.

The eye corrosive/irritating potential is confirmed by the other available study results performed on rabbits.

In the opinion of eMSCA, 4-TBC fulfils CLP classification criteria as a corrosive substance category 1.

7.9.3. Sensitisation

7.9.3.1 Skin

7.9.3.1.1 Non-human information

The Registrants provided three *in vivo* skin sensitisation studies. These data include results of LLNA, GPMT and method with the Landsteiner technique as modified by Draize and further modified by Hood.

In a dermal sensitization study using the method of Local Lymph Node assay (LLNA) (registration dossier, study 2003) with 4-TBC 85% in water, 9-week CBA/J mice (4 females per group) were tested according to the guideline OECD 429, at the concentrations of 1%, 2.5%, 5% and 25% in a mixture ethanol/water (1:1) as vehicle. The positive control group received alpha-hexylcinnamaldehyde (25%). The study was a GLP-compliant.

No mortality and no systemic clinical signs were observed during the study. Dryness of the skin was noted on day 6 on the ears of the animals given the concentration of 5%. In addition, a moderate or severe increase in ear thickness was recorded in the animals given the test substance at the concentrations of 2.5 and 5%, respectively.

A dose-related increase in the stimulation indices (SI) (SI = 15.35 / 47.05 / 63.26 at 1% / 2.5% / 5% respectively) was noted and the threshold positive value of 3 was exceeded at all tested concentrations. In the absence of local irritation, the positive lymphoproliferative response observed from the concentration of 1% could be attributed to delayed contact

hypersensitivity. However irritation effects were observed at concentrations above 1% and the evaluation of skin sensitization was made at the only concentration of 1% for which no increase in ear thickness was observed.

In this study, 4-TBC was a dermal sensitizer.

In a dermal sensitization study with 4-TBC in propylene glycol / acetone (90/10%), Dunkin-Hartley guinea pigs (24 females) were tested under test conditions similar to the guideline OECD TG 406 (GPMT). The positive control group received 2-methylol phenol. GLP compliance of these study was not specified.

On day 1, three intradermal injections were performed in a row on each side of the shoulder. 24 hours before the topical sensitization (day 7), all the animals were treated on the shoulder with a preparation consisting of sodium lauryl sulphate (SLS) 10% in dimethyl acetamide/acetone/ethanol. On day 8, topical sensitization on the same skin area was then performed with a solution of the suspected sensitizer. The patch was covered by an occlusive dressing for 48 hours. On day 22 (= Challenge I), a 24 -hour occluded patch was performed on the right flank with 25µl of TBC, 2 patches near the back. Challenge II was performed at the same time as challenge I but on the left side of the flank.

The concentrations used for induction phase were 3.40% (intradermal) and 16.7% (topical) and those used for challenge phase were 7.50% (challenge I) and 10% (challenge II). In challenge I, 20/24 (83%) treated animals showed positive reactions. In challenge II, 18/24 (75%) treated animals showed positive reactions. In this study, 4 -tert-butylpyrocatechol was a skin sensitizer.

In in vivo study carried out using the Landsteiner technique modified by Draize and further modified by Hood where guinea pigs were induced and treated with 1% of 4-TBC in propylene glycol. None of animals was sensitized by these method, but due to major methodological deficiencies the study was disregarded.

7.9.3.1.2 Human information

Several well controlled studies in workers (Estlander, 1998; Fardal, 1993; Gellin, 1970; Hillen, 2001, Hillen, 2003; Minamoto, 2002; Zimerson, 1999) were reported by the registrant. In those studies 4-TBC exerts skin sensitization activity with a variable incidence. Some studies showing a low incidence of positive skin reactions among workers are inconclusive but other studies demonstrate that all individuals tested using a patch-test technique develop positive reactions.

Overall conclusion on skin sensitisation

Based on the positive results of the LLNA and GPMT study and the observations in humans 4-TBC should be classified as a skin sensitizer according to the criteria of the Regulation (EC) No 1272/2008.

The reported LLNA study is showing a Stimulation Index ≥3 at all tested concentrations (1%, 2.5%, 5%). Therefore EC3 value ≤2% was obtained. Hence, the CLP criteria for the subcategory 1A of skin sensitisation of 4-TBC are fulfilled.

Taking into account that concentrations ≤1 % intradermal induction dose were not tested in the GPMT, results of this study are not sufficient for sub-categorisation of skin sensitisation classification of 4-TBC.

In conclusion, based on reliable and GLP-compliant LLNA study (registration dossier, study 2003) strong potency to skin sensitisation of 4-TBC can be confirmed and it should be classified as Skin Sens. 1A, H317.

7.9.4. Repeated dose toxicity

Not assessed.

7.9.5. Mutagenicity

Not assessed.

7.9.6. Carcinogenicity

Not assessed.

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

Not assessed.

7.9.8. Hazard assessment of physico-chemical properties

Not assessed.

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

Selection of the critical DNEL for Workers

DNEL Long term exposure - systemic effects - worker

Determination of the human DNEL for inhalation route have been derived by the registrants based on rat oral study.

The 14-week rat dietary toxicity study, where LOAEL was 781 ppm (equivalent to 70 mg/kg), was selected by registrants for DNEL derivation. The relevant systemic effects considered to bear a threshold mode of action were the changes in hematology and clinical chemistry seen at all dose levels. Forestomach lesions also observed in the study was considered to be of limited relevance - not relevant to humans.

The starting point was converted using an oral-to-inhalation route extrapolation. The registrant has assumed in oral-to-inhalation route extrapolation that absorption for both exposure routes is 100%. $LOAEC_{worker}$ derived by registrant is 123.4 mg/m^3.

$DNEL_{worker}$ derived by registrant is 1.6 mg/m^3

The eMSCA notes that according to the same study, in which the excretion of [14C]-p-tert-butylcatechol administered to rats by gavage were analysed, approximately 90% of the radiolabel was recovered in the urine. eMSCA proposes to use precautionary principle and assume that absorption following oral exposure in rat is 90%.

In such a case LOAEC and DNEL for worker for inhalation route should be as follows:

$LOAEC_{worker}$ = 70 x (1/0.38) x (6.7/10) x (90/100) = 111.1

$DNEL_{worker}$ 111.1/75 = 1.48 mg/m^3

Selection of the critical DNEL for general public (Indirect exposure of humans via the environment)

DNEL Acute / short-term exposure - systemic effects - oral route of exposure – man via environment

The oral rat acute toxicity study, where LOAEL was 490 mg/kg, was chosen by the registrants for DNEL derivation. The relevant systemic effects are the following clinical signs: decreased activity, piloerection and dyspnea.

No modification of the starting point is applied as the routes and duration of exposure are generally the same in both species.

DNEL Acute/short-term exposure - systemic effects - oral route of exposure for man via environment derived by registrants is 1.6 mg/kg bw.

The registrants considered observed effects (decreased activity, piloerection and dyspnea) as systemic effects. eMSCA notes that substance is classified as skin corr. 1B and eye damage category 1 and therefore decreased activity, piloerection can be secondary to local GI tract effects and should be considered as part of the local effects. The eMSCA asked registrant for the report from this study. Autolysis and ulceration of the stomach observed in dead animals would suggest a corrosive effect. Moreover eMSCA notes that it is likely that dyspnea is a gavage-relating complication. According to provided report dyspnea was observed in each animal which was not in coma. eMSCA concludes that it is not possible to establish LOAEL for systemic effect based on provided information from this study.

The eMSCA agrees with the statement of the registrants included in CSR that for local effects, the corrosive effects observed should be considered as the most important hazard and qualitative risk assessment should be performed for the local effects.

The eMSCA recommends the registrants to perform qualitative risk assessment for this endpoint and all acute endpoint: medium hazard due to classification Skin corrosion Category 1B in CLP, Serious eye damage Category 1 in CLP.

DNEL Long term exposure - systemic effects – for inhalation route of exposure - man via environment

The 14-week rat dietary toxicity study (US NTP, 2002), where LOAEL was 781 ppm (equivalent to 70 mg/kg), was selected by the registrants for DNEL derivation. The starting point was converted using an oral-to-inhalation route extrapolation. The registrants assumed in oral-to-inhalation route extrapolation that absorption for both exposure routes is 100%.

$LOAEC_{humans\ via\ environment}$ (24 h) derived by registrant is 60.9 mg/m^3

DNEL: Human via environment - DNEL long-term for inhalation route-systemic derived by the registrants is 406 µg/m3

The eMSCA notes that according to US NTP (2002) study, in which the excretion of [14C]-p-tert-butylcatechol administered to rats by gavage were analysed, approximately 90% of the radiolabel was recovered in the urine. The eMSCA proposes to use precautionary principle and assume that absorption following oral exposure in rat is 90%.

In such case LOAEC and DNEL for general population for inhalation route should be as follows:

$LOAEC_{humans\ via\ environment}$ (24 h) = 70 x (1 / 1.15) x (90/100) = 54.81 mg/m^3

DNEL for man via environment long-term for inhalation route-systemic = 54.81/150 = 365 µg/m3.

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

Hazard Class and Category Codes	Hazard Statement Codes
Acute Tox. 4	H302
Acute Tox. 4	H312
Skin Corr. 1 B	H314
Eye Dam. 1	H318
Skin Sens. 1A	H317

Justification of human health classification:

Acute Oral toxicity

The oral LD_{50} in male and female rats (Sprague-Dawley) in the key study was 815 mg/kg bw, what triggers classification. Supporting study provided similar oral LD_{50} values (817 - 821 mg/kg bw).

4-TBC should therefore classified as Acute Tox. 4, H302: Harmful if swallowed (Acute Tox. 4, H302), according to the CLP Regulation/UN GHS, based on the main values obtained for oral LD_{50}.

Acute Dermal toxicity

Four studies are available, two on rats and two on rabbits. The dermal LD_{50} was 1331 mg/kg and >2003 mg/kg for rats.

Tests results of two studies for rabbits are more severe and LD_{50} 630 mg/kg bw was obtained in both of them. However, one of the studies was not used for the classification by the eMSCA, since its reliability is 3.

4 -tert-butylpyrocatechol is classified as Acute Tox. 4, H312: Harmful in contact with skin (Acute Tox. 4, H312), according to the CLP Regulation/UN GHS, based on the value of LD_{50} 1331 (unpublished study, 1992).

Skin corrosion/irritation

According to CLP criteria a corrosive substance is a substance that produces destruction of skin tissue, namely, visible necrosis in at least 1 tested animal after exposure up to a 4 hour duration.

There are two tests on New Zealand White rabbits supporting classification of 4-TBC as corrosive category 1B, H314. Both studies were considered by eMSCA as reliable.

Serious eye damage/eye irritation

Two available tests on rabbits confirm properties of the substance as inducing irreversible effects on eyes.

Skin sensitization

Based on reliable and GLP-compliant LLNA study strong potency to skin sensitisation of 4-TBC can be confirmed and it should be classified as Skin Sens. 1A, H317.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

No data regarding potential ED properties for environment are available in the registration dossier, as well as in the available data base, therefore the information on human health is considered in the evaluation.

7.10.2. Endocrine disruption - Human health

The assessment of an ED properties for human health was performed according to the OECD Conceptual Framework for the Testing and Assessment of Endocrine Disrupters (https://www.oecd.org/env/ehs/testing/OECD%20Conceptual%20Framework%20for%20Testing%20and%20Assessment%20of%20Endocrine%20Disrupters%20for%20the%20public%20website.pdf).

That assessment indicates that 4-TBC is negative in most tests except the uterotrophic assay.

The low-level ED evaluation of 4-TBC shows negative or very weak estrogenic activity predicted in the QSAR and ToxCast model as well as in vitro bioassays (receptor binding and yeast assay).

In the repeated dose 90-day oral toxicity study on rats and mice performed according to OECD Guideline 408 and GLP principles with reliability 1 (at dose levels ranging from 781 to 12500 ppm) there were no clinical signs of toxicity except of decrease of body weights at the highest dose groups.

In the registration dossier the results of two studies (on rats and mice) investigating toxicity to reproduction are available (GLP compliant and comparable to an OECD Guideline). Following 14 weeks of dietary administration to rats (at dose levels ranging from 3125 to 12500 ppm) there were no clinical signs of toxicity except of decrease of body weight in the exposed rats.

The weight of epididymis and testis and the number of spermatids per testis and epididymal sperm motility of males in the highest group were less than in control group. The number of females with regular estrous cycle were decreased in the highest groups. Exposed females had less estrous cycle compared to control. Estrous cycle length increased with increasing concentration of 4-TBC.

No clinical signs of toxicity were observed in mice. Mean body weights of mice exposed to highest concentration of 4-TBC were lower than in control. There were no effects on reproductive organs, sperm count or motility in males. Females of the highest group had a longer estrous cycle compared to control group.

The results of prenatal developmental toxicity study on rats (OECD Guideline 414 and GLP with reliability 1) at the dose ranging from 10 to 100 mg/kg bw/d, indicate maternal toxicity in 100 mg/kg group. Five females of this group were found dead and all deaths were

considered to be associated to the treatment. At the same dose there were body weights loss compared to control due to a marked decrease of mean food consumption.

There were no treatment-related findings at macroscopic post-mortem examination. Females of the highest exposed group had lower mean gravid and carcass weight. In the same group the increased number of dead foetuses was insignificant and a tendency towards dose-related increase of post-implantation loss was within the historical data.

At the highest group there was a slight decrease in mean fetal body weight considered to be of minor toxicological significance. At this group an increased litter incidence of foetuses with autolysis was found, however similar finding was noted in the control group. The observed increase in the number of fetuses with ossification delays was considered to be associated to the treatment but of minor significance. Developmental symptoms occur with maternal toxicity. There were no malformations at tissue examination.

7.10.3. Conclusion on endocrine disrupting properties

Several assays and studies regarding an ED potential are available for 4-TBC.

The computational prediction and test results suggest that 4-TBC has very weak or weak estrogenic activity. Based on the publication of Miller et al (2001) the affinity of 4-TBC to estrogen receptor is about 3 000 000 times lower compared to estradiol. The substance was positive in only one assay investigating the relationship between the results of in vitro and in vivo receptor binding assays in comparative study with selected chemicals.

In the reproductive toxicity tests no ED-related effects were observed and there was no evidence of a reproductive effect in any of the parameters examined. Effects observed in some studies, such as increased estrous cycle length, reduced number estrous cycle in exposed females, lower weight of epididymis and testis raise some concern for potential endocrine disruption, however the available data is not sufficient to conclude.

7.11. PBT and vPvB assessment

Persistence

Based on the available screening data, the eMSCA concludes that 4-TBC should be regarded as biodegradable in water, sediment, and soil in the context of environmental assessment under REACH. It is not considered to meet the P or vP criteria.

Bioaccumulation

Based on the available screening data (log Kow 1.98, log Koa 10.2), 4-TBC is not bioaccumulative in aquatic and air-breathing organisms.

Toxicity

4-TBC does not fulfil currently the toxicity criterion. The lowest aquatic toxicity endpoint for 4-TBC is more than 0,01 mg/l. Furthermore, this substance is not classified as a CMR (on the basis of available data). However, studies are on the way to address reproductive toxicity and mutagenicity. Therefore the assessment of the toxicity criterion and the conclusion "not T" is only preliminary.

Overall conclusion on the PBT/vPvB assessment

The PBT criteria of REACH Annex XIII are not fulfilled based on the currently available data. The evaluating eMSCA overall concludes that 4-TBC is not a PBT or vPvB substance.

7.12. Exposure assessment

7.12.1.1. Worker

The eMSCA has a number of reservations regarding assessment of inhalation exposure for workers (quantitative), provided by the registrants.

In most CSRs there are no estimations for full work shift. There is no RCR calculated for the whole ES but only for each task separately. The eMSCA doubts that every task is performed by different workers. The eMSCA notes that an 8-hour time-weighted average will be higher than value estimated for one task and it may lead to unacceptable level of exposure.

In all CSRs there is lack of exposure scenario for certain potential tasks.

In the CSRs incorrect input data in ECETOC TRA are used. Furthermore, incomplete input data for exposure estimation are provided. That is why the eMSCA recommends that the registrants revise their exposure assessment. The main recommended correction includes consideration of higher temperature in estimation when appropriate and estimation for full work shift. The eMSCA notes that revised exposure assessment may lead to higher estimated values and in consequence to unacceptable level of exposure.

7.12.1.2. Consumer

Not assessed.

7.12.2. Environment

eMSCA concludes that 4-TBC should be regarded as biodegradable in water, sediment, and soil and because of this does not persist a long time in the environment.

According to available information 4-TBC has a low potential for bioaccumulation, so its accumulation through the food chain or secondary poisoning is unlikely.

Significant reduction of the incidence in the environment may take place through substance incineration or landfill in biological sewage treatment plant that is declared in several ES. In some scenarios no direct water or soil releases are considered. Environmental exposure estimates are mainly based on EUSES (versions 3.1; 3.3) included in the CHESAR software and EasyTRA 2.0. which complies with EU TGD 2003 Risk Assessment Spreadsheet Model 1.24a.

7.13. Risk characterisation

Human Health

Workers

In consequence of the recommended revision of the exposure assessment (see section 7.12), the quantitative risk characterisation would also need to be revised by the registrants in the CSRs.

Indirect exposure of humans via the environment.

For quantitative risk characterization of 4-TBC, exposure data from inhalation exposure were compared with the DNEL for man via environment long-term for inhalation route-systemic derived by the eMSCA (refer to section 7.9.9). However, lower DNEL (derived by eMSCA) do not result in RCR >1 in any ES.

The eMSCA notes that in one ES: Use in laboratories the registrant does not recommend eye protection. Since substance is classified as eye damage category 1, therefore the eMSCA suggest that the registrants revise their recommended RMM and include also eye protection in ES: Use in laboratories.

Environment

The comparison of PECs to the relevant PNECs, calculated by the eMSCA, leads to the conclusion that risk for the environment posed by 4-TBC is controlled. All the RCR values are < 1 indicating a low potential for adverse effects in the environment, when the conditions of use in the exposure scenario are applied.

The eMSCA concludes that there are no reasons for concern that need to be addressed.

7.14. References

Estlander T., Kostiainen M., Jolanki R., Kanerva L. 1998: Active sensitization and occupational allergic contact dermatitis caused by para-tertiary-butylcatechol , Contact Dermatitis, 38(2), 96-100.

Fardal RW, Curphey ER 1983: Phototypesetting paper as a cause of allergic contact dermatitis in newspaper production workers, Cutis, Cutaneous Medicine for the Practitioner, 31(5), 509-512, 515, 517.

Gellin GA, Passick PA, Perone VB 1970: Depigmentation from 4-Tertiary Butyl Catechol - An Experimental Study (publication), J Investigative Dermatology, 55(3), 190-197.

Hans Peter Arp, Preliminary assessment of substances registered under REACH that could fulfil the proposed PMT/vPvM criteria, BACKGROUND DOCUMENT TO THE WORKSHOP: "PMT AND vPvM SUBSTANCES UNDER REACH" MARCH 13'TH-14'TH. BUNDESPRESSEAMT, BERLIN, GERMANY; DOC.NO. 20160426-TN-01; 2018-03-06

Hillen U., Frosch PJ., John SM., Pirker C., Wundenberg J. and Goos M. 2001: Patch test sensitization caused by para-tertiary butylcatechol. Results of a prospective study with a dilution series., Contact Dermatitis, 45(4), 193-196.

Hillen U, Frosch PJ, Franckson T, Pirker C and Goos M 2003: Optimizing the patch-test concentration of para-tertiary-butylcatechol: results of a prospective study with a dilution series, Contact Dermatitis, 48, 140-143.

Miller et al, Estrogenic Activity of Phenolic Additives Determined By an In Vitro Yeast Bioassay, Environmental Health Perspectives, Vol. 109: 2, 2001,

Minamoto K., Nagano M., Inaoka T. and Futatsuka M. 2002: Occupational dermatoses among fibreglass-reinforced plastics factory workers, Contact Dermatitis, 46(6), 339-347.

NTP Technical Report, NTP Technical Report on the Toxicity Studies of p-tert-Butylcatechol, 2002,

Registration Dossier 2017.

Zimerson E, Bruze M and Goossens A 1999: Simultaneous p-tert-butylphenol-m-formaldehyde resin and p-tert-butylcatechol contact allergies in man and sensitizing capacities of p-tert-butylphenol and p-tert-butylcatechol in guinea pigs (publication), J.

Occupational Environmental Medicine, vol. 41, number 1, 23-28.

Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health Version: 2.1, November 2012

Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0, July 2017

ECHA Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017)

ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017)

7.15. Abbreviations

C&L - Classification and labelling

CLP – Classification, Labelling and Packaging

CoRAP – Community Rolling Action Plan

CSR – Chemical Safety Report

DMEL - Derived Minimal Effect Level

DNEL – Derived No Effect Level

ECETOC - European Centre for Ecotoxicology and Toxicology of Chemicals

ECHA – European Chemical Agency

EC3 - the concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation

ES – Exposure Scenario

EU – European Union

eMSCA – Evaluating Member State

EPA – Environmental Protection Agency

GLP – Good Laboratory Practice

LD – Lethal Dose

LC – Lethal Concentration

LLNA - Local lymph node assay

LOAEL – Lowest Adverse Observed Effect Level

LOAEC - Lowest Adverse Observed Effect Concentration

MSCA – Member State Competent Authority

NOAEC - No Observed Adverse Effect Concentration

NOAEL – No Observed Adverse Effect Level

NTP - National Toxicology Program

PBT – Persistent, Bioaccumulative, Toxic

(Q)SAR - Quantitative structure–activity relationship

RAR – Risk Assessment Report

RCR – Risk Characterisation Ratio

RMM - Risk Management Measures

SVHC – Substance of Very High Concern

TG – Test Guidance

vPvB – very Persistent, very Bioaccumulative