baua:
Bundesanstalt für Arbeitsschutz und Arbeitsmedizin
Federal Institute for Occupational Safety and Health

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

4-*tert*-butylphenol (ptBP)

EC No 202-679-0

CAS RN 98-54-4

p-(1,1-dimethylpropyl)phenol (ptAP)

EC No 201-280-9

CAS RN 80-46-6

Evaluating Member State(s): Germany

Dated: 29 November 2023

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2014

Before concluding the substance evaluation a Decision to request further information was issued for both substances on: 20 April 2016

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 registrants 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 Registrants 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

Both substances ptBP and ptAP were originally selected for substance evaluation (SEv) in order to clarify concerns about:

- endocrine disruption (ED) for the environment
- high (aggregated) tonnage

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

- repeated-dose toxicity (RDT; female reproductive tract, nephrotoxicity, systemic depigmentation/vitiligo and thyroid function)
- ED for human health
- exposure of workers
- exposure of consumers

During the evaluation also other concerns were identified for ptBP only. The additional concern was:

- developmental toxicity

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A risk assessment report (RAR) for ptBP was published in 2008 according to the Existing Substances Regulation 793/93/EEC. The substance was included in Annex VI of the CLP Regulation and classified for its effects on sexual function and fertility (Repr. 2, H361f), skin, eye and respiratory irritation as well as aquatic toxicity (see Section 7.6.1).

Risk Management Option Analyses (RMOA) were carried out for both ptBP (DE CA, 2015a) and ptAP (DE CA, 2015b) by the evaluating Member State Authority (eMSCA) in 2015. Assessing possible risk management options in the light of the concern of ED properties for the environment, the eMSCA determined the identification as substances of very high concern (SVHC) as the most appropriate risk management option. Both substances were identified as SVHC according to Art. 57 (f) based on ED properties for the environment prior to conclusion of the substance evaluation (ECHA, 2016a; ECHA, 2016d), and by July 2019, they were included in the candidate list[2]. Depending on the information on relevant sources of exposure for ptBP and ptAP, triggered by SVHC identification, the eMSCA proposes that a future restriction of the corresponding uses to limit these emissions may be considered necessary.

In 2021 ECHA published an assessment of regulatory needs (ARN) for substances containing ptBP (ECHA, 2021). In this ARN, ECHA investigated a group of alkylphenols containing ptBP as a constituent or as an impurity. ECHA suggested a need for a restriction for ptBP as a substance, constituent or impurity in other substances, mixtures and articles in order to ensure that environmental emissions are minimised.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the eMSCA to the following conclusions, as summarised in the Table 1 below.

[2] https://echa.europa.eu/de/candidate-list-table

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) – ED Env	x
Restrictions	x
Other EU-wide measures	x
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

It is noted that since the substances ptBP and ptAP have been identified as SVHC based on REACH article 57f due to their ED properties for the environment, both substances are anticipated to fulfil the criteria for ED Cat. 1 according to the amended CLP Regulation (Commission Delegated Regulation (EU) 2023/707 of 19 December 2022).

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

The concern for being ED for the environment was substantiated for ptBP and ptAP as a consequence of the evaluation. The eMSCA prepared a RMOA (DE CA, 2015a; DE CA, 2015b) and subsequently submitted Annex XV proposals to identify ptBP and ptAP as substances of very high concern due to their ED properties for the environment in August 2016 (DE CA, 2016a; DE CA, 2016b). Both substances were identified as SVHC according to Art. 57 (f) – ED for the environment (ECHA, 2016a; ECHA, 2016d) and by July 2019, were included in the candidate list[2].

As to human health, the requested studies under SEv (see Section 7.2) did not further inform on RDT or ED effects for human health of both substances. However, based on the available data, ptBP and ptAP (via read-across) might fulfil the criteria for ED for human health according to the amended CLP Regulation.

4.1.3. Restriction

Already during the formal SEv procedure, ptBP and ptAP have been identified as substances of very high concern based on proposals by the eMSCA due to their ED properties for the environment. Based on the hazardous properties of ptBP, the need for a restriction has been identified by ECHA for a group of alkylphenols which also included these two

substances (ECHA, 2021). Both substances were included in the EU restriction roadmap although the scope is not yet clear[3].

The potential need for a restriction has also been previously touched upon in an RMOA conducted by the eMSCA (DE CA, 2015a; DE CA, 2015b). However, further exposure data would need to be collected to improve the database for the whole substance group in terms of e.g. emissions, uses, impact on society etc. for a potential restriction proposal. The uncertainties related to the concern for human health could potentially also be further addressed in such a restriction proposal.

4.1.4. Other EU-wide regulatory risk management measures

Based on the ptBP-induced systemic depigmentation/vitiligo in workers, the German MAK-Commission[4] proposed in 1981 a MAK value of 0.5 mg/m^3 ptBP as a health-based occupational exposure limit (OEL) at the workplace (MAK, 1981-1995). Subsequently, 0.5 mg/m^3 was adopted by the German Committee on Hazardous Substances ("Ausschuss für Gefahrstoffe", AGS)[5] as a legally binding occupational exposure limit (OEL) in Germany ("Arbeitsplatzgrenzwert", AGW) and published in Technical Rule for Hazardous Substances ("Technische Regeln für Gefahrstoffe", TRGS) No. 900[6]. In its supporting documentation, the MAK-Commission discussed several limitations and uncertainties of the proposed OEL of 0.5 mg/m^3 and considered this value of provisional nature. Currently, a European OEL has not been established for either ptBP or ptAP (which is also known to cause vitiligo). Nevertheless, for ptBP several European countries have adopted an OEL of 0.5 mg/m^3 as an 8 h-TWA.

Therefore, an EU-wide regulatory measure for a binding OEL (BOEL) should be pursued. The eMSCA considers that setting of a BOEL at EU level would improve the risk management of the substances in occupational uses.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS

Indication of a tentative plan is not a formal commitment by the eMSCA.

[3] https://ec.europa.eu/docsroom/documents/49734/attachments/1/translations/en/renditions/native
[4] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area; https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/index.html
[5] The advisory body of the Federal Ministry of Labour and Social Affairs (BMAS) on the Ordinance on Hazardous Substances https://www.baua.de/DE/Die-BAuA/Aufgaben/Geschaeftsfuehrung-von-Ausschuessen/AGS/AGS_node.html
[6] http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/TRGS-900.html

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Annex XV dossier for SVHC identification as ED ENV	*06/2016*	*eMSCA*
Restriction	*TBD*	*TBD*
Health-based occupational exposure limit (BOEL)	*TBD*	*TBD*

For the potential work on a restriction proposal, a timeline cannot be indicated at this stage (see 4.1.3).

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Both substances ptBP and ptAP were originally selected for substance evaluation in order to clarify concerns about:

- ED for the environment
- high (aggregated) tonnage

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

- RDT (female reproductive tract, nephrotoxicity, systemic depigmentation/vitiligo and thyroid function)
- ED for human health
- exposure of workers
- exposure of consumers

During the evaluation also other concerns were identified for ptBP only. The additional concern was:

- developmental toxicity

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Endocrine disruptor – environment	**Concern confirmed.** SVHC (Art. 57f) as ED for environment confirmed (2019).
Repeated dose toxicity (effects on female reproductive tract; nephrotoxicity; systemic depigmentation/vitiligo; effects on thyroid function)	**Concern unresolved** for both ptBP and ptAP. Concerns related to nephrotoxicity, systemic depigmentation and melanocyte destruction (including in the eyes and inner ear cochlea) and effects on the thyroid function unresolved. A further study using a non-albino rat strain is not requested due to proportionality and animal welfare considerations.

	Effects on the female reproductive tract sufficiently addressed in the existing 90-day study.
Endocrine disruptor - human health	**Concern unresolved with regard to potential autoimmune thyroid effects** (see RDT) for both ptBP and ptAP.
Occupational (Worker) exposure	**Concern clarified** for both ptBP and ptAP. The identified risks that arose from exposure assessment of dermal and inhalation exposure to ptBP and ptAP concerning the use of molten substances and use of the substances as flakes were clarified by a higher tier assessment provided by the registrants and no further concerns remain. For ptBP, the identified risk with regard to dermal exposure for the application of liquid and solid end products containing ptBP as hardener in paints, adhesives, thinners etc. (up to 30 %) was clarified by a higher tier assessment by the registrants for ptBP and no further concerns remain.
Exposure of consumers	The lead registrants have indicated that neither ptBP nor ptAP are used as such or in mixtures by consumers. **Concern unresolved for** ptBP. Not all registrations have been updated accordingly. There are still some indications of continuing consumer use (ECHA, 2021). In addition, consumer exposure may occur via ptBP in other substances and via residual monomers present in articles manufactured from ptBP. **Concern clarified for** ptAP. All registration dossiers have been amended accordingly.
Developmental toxicity	**Concern clarified.** Read-across between ptBP and ptAP is considered acceptable with regard to the developmental toxicity data gap (study according OECD TG 414) on ptBP. There is no developmental toxicity relevant for classification.

7.2. Procedure

On 31 May 2013, ptBP and ptAP were proposed for SEv in compliance with article 44(1) of the Regulation (EC) No 1907/2006 (REACH Regulation). The substances were identified by the German eMSCA as of high environmental concern. On 26 March 2014, ECHA published the CoRAP and initiated substance evaluations for ptBP and ptAP. Both substances ptBP and ptAP were brought forward for discussions in the 3rd and 12th meeting ED expert group (EG) by the eMSCA.

In the course of the substance evaluations the eMSCA considered all data available until October 2014 and identified additional concerns for both substances regarding RDT and occupational exposure. The concern for environmental ED could be clarified during the evaluation year. For environmental endpoints, the substance evaluation was concluded in March 2015 based on the available information in the registration and scientific literature up to this date. The eMSCA considered the clarification of this specific concern possible based on the available information without the need to request further information from the registrants via a decision. Registration updates after this date were not taken into account for the result of the evaluation with regards to this particular endpoint. Both substances were identified as SVHC according to Art. 57 (f) – ED for the environment already before the formal conclusion of the SEv process (ECHA, 2016a; ECHA, 2016d), and by July 2019, they were included in the candidate list[2].

In order to clarify the remaining human health concerns for RDT (both substances) and for developmental toxicity (for ptBP only), substance evaluation decisions with additional information requirements were finalised and sent to the registrants on 20 April 2016 (ECHA, 2016b; ECHA, 2016c).

The concerns for RDT were required to be addressed with a modified OECD TG 408 to report on effects regarding nephropathy, effects on the female reproductive tract, systemic depigmentation and thyroid function. As an alternative, the registrants were given the possibility to provide the results of an existing repeated dose toxicity study (90-day) conducted using ptAP. In addition, the registrants were requested to provide additional information necessary to refine the risk assessment for worker exposure.

In the follow-up, registrants provided a higher tier assessment for worker exposure scenarios and a 90-day oral RDT study performed with ptAP (performed according to EPA OPPTS 870.3100) and updated the lead registration in April 2018 accordingly. The eMSCA considered this new information provided for the present substance evaluations. The concern for occupational exposure raised in that decision was addressed by the registrants.

The eMSCA considered the toxicological information provided as being sufficient to address the concern on effects on female reproductive organs. However, the eMSCA concluded that information from that study did only in part fulfil the requests of decision as that study was performed in albino animals and was insufficient with respect to the additional concerns i.e. nephropathy, systemic depigmentation including potential effects on eye and ear, and thyroid function. As these concerns were still present, they were addressed in a second draft decision.

However, following the exchange with registrants and ECHA on the second set of draft decisions, the eMSCA decided to stop the decision-making process under substance evaluation based on considerations of animal welfare, proportionality and already implemented risk management measures. The substance evaluation was terminated in January 2023.

As ptBP and ptAP have been identified as substances of very high concern based on their ED properties for the environment following proposals submitted by the eMSCA, further information requirements to clarify the remaining concerns are not considered proportionate by the eMSCA at the current stage. For ptAP, only industrial uses are still registered. Furthermore, based on the hazardous properties of ptBP, the need for a restriction has been identified by ECHA for a group of alkylphenols including these two substances (ECHA, 2021). The potential need for a restriction has also been previously touched upon in a RMOA conducted by the eMSCA (DE CA, 2015a; DE CA, 2015b) and 4.1.3).

Hence, the eMSCA considers that the current and envisaged risk management measures will sufficiently minimise the potential risks arising from the remaining concerns. In view of these developments and considering the fact that new cases of occupational vitiligo were not recorded in Germany since the enforcement of MAK occupational exposure limit values, it is not currently considered justified to uphold the requirement for additional animal testing.

7.3. Identity of the substance

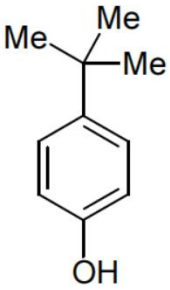
Table 4

SUBSTANCE IDENTITY		
Public name:	4-*tert*-butylphenol	*p*-(1,1-dimethylpropyl)phenol
EC number:	202-679-0	201-280-9
CAS number:	98-54-4	80-46-6
Index number in Annex VI of the CLP Regulation:	604-090-00-8	N/A
Molecular formula:	$C_{10}H_{14}O$	$C_{11}H_{16}O$

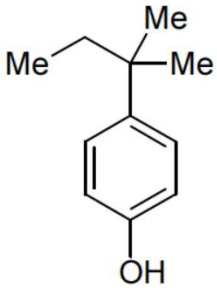
Molecular weight range:	150.2176 g/mol	164.24 g/mol
Synonyms:	4-(1,1-dimethylethyl)phenol Phenol, *p*-*tert*-butyl- (8CI) 4-(1,1-Dimethylethyl)phenol 4-*tert*-Butylphenol Butylphen NSC 3697; *p*-*tert*-butylphenol *p*-*tert*-Butylphenol ptBP	4-(1,1-dimethylpropyl)phenolPhenol, *p*-(1,1-dimethylpropyl)- (5CI); Phenol, *p*-*tert*-pentyl- (6CI,8CI); 4-(1,1-Dimethylpropyl)phenol; 4-*t*-Amylphenol; 4-*t*-Pentylphenol; 4-*tert*-Amylphenol; 4-*tert*-Pentylphenol; Amilfenol; BirexSE; NSC 403672; NSC 4965; *p*-(1,1-Dimethylpropyl)phenol; *p*-(α,α-Dimethylpropyl)phenol; *p*-*tert*-Amylphenol; *p*-*tert*-Pentylphenol ptAP

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

Structural formula:



ptBP



ptAP

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES		
Property	**Value for ptBP**	**Value for ptAP**
Physical state at 20°C and 101.3 kPa	white flakes with a phenolic odour (visual and olfactory inspection)	slightly yellow solid (flakes) with a phenolic odour
Melting/freezing point	99.2 °C at 101325 Pa	94.7 °C at 101325 Pa
Boiling point	238 °C at 101325 Pa	255 °C at 101325 Pa
Vapour pressure	0.5 Pa at 20 °C	< 5 Pa at 20 °C (Method NFT 20-048, Isoteniscope; Conte T 2012)
Water solubility	607.2 mg/L at 25 °C, pH = 6 – 7	193 mg/L at 21 °C, pH 6 – 7

	(ASTM E 1148 – 02; flask method)	(ASTM E 1148 – 02; flask method)
Partition coefficient n-octanol/water (Log Kow)	3.0 at 23 °C, pH = 5.7 (OECD Guideline 117, HPLC method)	logPow 3.6 at 22 °C, pH 6 – 7 (OECD TG 117, HPLC method)
Granulometry	In accordance with column 2 of REACH Annex VII not required: substance is marketed or used in a non-solid or granular form	In accordance with column 2 of REACH Annex VII not required: substance is marketed or used in a non-solid or granular form
Stability in organic solvents and identity of relevant degradation products	The stability in organic solvents is considered not to be critical.	The stability in organic solvents is considered not to be critical.
Dissociation constant	pKa = 10.13 (QSAR estimation)	In accordance with section 1 of EC 1907/2006 Annex XI, the dissociation constant study does not need to be performed as calculations with SPARC online calculator have shown that there is no dissociation in the range between pH -0.2 and 14.

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR) FOR ptBP				
☐ 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

Table 7

AGGREGATED TONNAGE (per year) FOR ptAP				
☐ 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

7.5.2.1. Uses of ptBP

ptBP is used as an intermediate during hydrogenation, manufacture of derivatives, polycarbonate production and as a monomer in the production of formaldehyde and epoxy resins. Additionally, ptBP is used as a hardener up to 30 % for paints, adhesives, putties, thinners etc. According to the lead registrant the end uses of ptBP as a hardener in coatings and paints, fillers, putties, thinners take place exclusively in the industrial sector and there are no professional uses of ptBP as a pure substance or in mixtures. The eMSCA considers

that the industrial uses such as polymers and coating products, building and construction work (described on the dissemination site of ECHA for ptBP) in many cases also indicate applications in the professional field. This could be taken into account and further information gathered in follow-up regulatory substance processes.

During the SEv procedure, some of the registrants including the lead registrant updated their registration dossier removing some industrial, all professional and all consumer uses. The removal of uses specifically related to scenarios where the substance occurs as a residual monomer (e.g. paints, lacquers and varnishes, construction materials, process regulators, adhesives, binding agents, fillers). Two registrants still support professional and consumer uses in their current dossier. However, the corresponding dossiers have not been updated for more than 10 years, i.e. even since before the start of the substance evaluation process. This leads to a discrepancy in uses listed between the ECHA dissemination site and uses that are not supported by the dossier of the lead registrant (Table 8 .

Table 8

Uses of ptBP	Use(s) dissemination site	Use(s) not supported by lead dossier
Uses as intermediate	na	na
Formulation	na	na
Uses at industrial sites	**Manufacture** of ptBP: Processes: transfer of chemicals, closed processes with no likelihood of exposure, closed, continuous processes with occasional controlled exposure, transfer of substance into small containers and laboratory work. **Formulation**: coating products, adhesives and sealants. Processes: transfer of chemicals, mixing in open batch processes, closed batch processing in synthesis or formulation, transfer of substance into small containers, closed processes with no likelihood of exposure and closed, continuous processes with occasional controlled exposure. **Industrial uses**: polymers and coating products (including end use as hardener with increased (>30%) residual ptBP content), building & construction work, intermediate, monomer in production of Mannich base, adhesives and sealants. Processes: transfer of chemicals, mixing in open batch processes, batch processing in synthesis or formulation with opportunity for exposure, transfer of substance into small containers, closed batch processing in synthesis or formulation, closed processes with no likelihood of exposure, closed, continuous processes with occasional controlled exposure and laboratory work.	na

Uses by professional workers	Adhesives and sealants and coating products. Processes: transfer of chemicals at non-dedicated facilities, roller or brushing applications, non-industrial spraying and transfer of substance into small containers.	Adhesives and sealants and coating products. Processes: transfer of chemicals at non-dedicated facilities, roller or brushing applications, non-industrial spraying and transfer of substance into small containers.
Consumer Uses	Consumer end use of adhesives Consumer application of coatings and paints.	Consumer end use of adhesives Consumer application of coatings and paints
Article service life	Use as an intermediate* Use of flakes as component of a coating additives* Use of articles incorporating materials where the substance is used as a hardener Use as a monomer in production of polymers – large scale* End use as hardener (e.g. in Coatings and Paints, Fillers, Putties, Thinners. Polymer Preparations and Compounds) with increased (< 30 %) residual ptBP content* Article service life of various articles treated with sealants used by (industrial) workers Use as a component of two-part coatings* Use as a monomer in production of polymers – small scale* Use of flakes as monomer in the production of Mannich bases*.	* most of these use titles appear in the lead dossier as "Workers uses in Industrial setting"

Note: na = not applicable.

7.5.2.2. Uses of ptAP

ptAP is used as a monomer in the production of phenolic resins and as an intermediate in the production of perfumes and fragrances. There are no downstream uses of ptAP itself or in preparations within the EU. However, the polymer (phenolic resins) is used for some applications.

During the SEv procedure all registrants including the lead registrant updated their registration dossier removing some industrial, all professional and all consumer uses.

Table 9 lists the uses of ptAP according to the ECHA dissemination site.

Table 9

Uses of ptAP	Use(s)
Uses as intermediate	na
Formulation	na
Uses at industrial sites	Polymers and intermediate in the production of perfumes and fragrances, chemicals and plastic products. Processes: transfer of chemicals, closed, continuous processes with occasional controlled exposure, transfer of substance into small containers, closed batch processing in synthesis or formulation, batch processing in synthesis or

	formulation with opportunity for exposure, mixing in open batch processes, closed processes with no likelihood of exposure and laboratory work.
Uses by professional workers	na
Consumer Uses	na
Article service life	na

Note: na = not applicable.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

As per Commission Regulation (EU) No 605/2014 of 5 June 2014 and as per Commission Regulation No 2018/1480 of 8 October 2018, amending Annex VI of Regulation (EC) No 1272/2008, ptBP is listed with the following harmonised classification:

Table 10

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)**		
604-090-00-8	4-tert-butyphenol	202-679-0	98-54-4	Skin Irrit. 2 Eye Dam. 1 Repr. 2 Aquatic Chronic 1	H315 H318 H361f H410	M(Chronic)=1	

For ptAP no harmonised classification is listed in Annex VI, Part 3, Table 3.1. of Regulation (EC) No 1272/2008.

7.6.2. Self-classification

For ptBP, the registrations adopt the harmonised classification from Annex VI CLP. For ptAP, the following hazard classes and precautionary statements is provided in the registrations:

Skin Corr. 1B	H314	Skin Sens. 1	H317
Eye Dam. 1	H318	Aquatic Chronic 1	H410.

In addition, the following hazard classes and precautionary statements are notified among the aggregated self-classifications in the C&L inventory:

Skin Corr. 1B	H314	Skin Corr. 1C	H314
Skin Sens. 1	H317	Eye Irrit. 2	H319
Resp. Sens. 1	H334	Acute Tox. 4	H302, H336, H370

STOT RE 1	H372	STOT SE	H335
Aquatic Chronic 2	H411	Aquatic Chronic 3	H412.

7.7. Environmental fate properties

The environmental fate properties were not assessed in detail and were later not relevant for the identification of ptBP and ptAP as SVHC in accordance with Art 57(f) of REACH.

7.7.1. Degradation

Degradation was not assessed in detail for ptBP and ptAP. For the scope of this assessment ptBP was assumed to be readily biodegradable, but failing a 10-day window.

7.7.2. Environmental distribution

Details on adsorption and desorption behaviour for ptBP and ptAP are included in the SVHC dossiers prepared for both substances (DE CA, 2016a; DE CA, 2016b).

Release of ptBP and ptAP will be mainly through wastewater treatment plants. From there the substances may enter the environment mainly via STP effluent and sludge application to soil. ptBP released into water will mainly remain in the water compartment and adsorb to sediment to a small amount. ptBP and ptAP released to soil will remain in soil almost completely. Therefore, the main compartments effected by ptBP and ptAP are water, soil and sediment.

7.7.3. Bioaccumulation

Not considered during this substance evaluation.

7.8. Environmental hazard assessment

For both substances environmental endpoints related to the concern of suspected ED in the environment and environmental exposure, the substance evaluation from the environmental hazard side was concluded after the initial 12-month evaluation period (i.e. in March 2015) and was therefore based on the available information in the registration and scientific literature up to that date. The eMSCA considered the clarification of this specific concern possible based on the available information without the need to require further information from the registrants of the substances via a decision. Registration updates after March 2015 were not taken into account for the result of the evaluation with regards to environmental endpoints.

Based on all available information, the eMSCA came to the conclusion that ptBP and ptAP fulfil the WHO criteria for an ED for the environment (see 7.10.1. for further details). Based on the WHO criteria, both substances were identified as SVHC due to their ED properties for the environment. Based on the new CLP hazard classes and their criteria, the eMSCA considers ptBP and ptAP are likely to fulfil a harmonised classification as ED Cat.1 for the environment.

7.8.1. Aquatic compartment (including sediment)

For information regarding aquatic toxicity, reference is made to the Annex XV SVHC dossier.

7.8.2. Terrestrial compartment

Not considered during this substance evaluation.

7.8.3. Microbiological activity in sewage treatment systems

Not considered during this substance evaluation.

7.8.4. PNEC derivation and other hazard conclusions

Not considered during this substance evaluation.

7.8.5. Conclusions for classification and labelling

The concern for being an ED for the environment was substantiated for ptBP and ptAP as a consequence of the evaluation. A SVHC-identification according to Art. 57 (f) was proposed for both substances in 2016. In July 2019 both substances were included in the candidate list based on their environmental ED properties.

7.9. Human Health hazard assessment

The substance evaluation with respect to human health focused on the concerns identified, i.e. RDT, ED for human health, and specifically for ptBP, developmental toxicity. Particular emphasis was given to the evaluation of RDT including depigmentation and vitiligo in humans. In Germany, vitiligo-like skin depigmentation after exposure to ptBP has been recognised as an occupational disease. Therefore, the eMSCA sent a questionnaire concerning entries in national registries of occupational diseases linked to ptBP across the EU. Some countries responded to this request. However, the data provided was of limited value within the scope of this evaluation.

In addition, because of an initially identified concern on ED for the environment based on an oestrogenic mode of action, particular emphasis was put on the evaluation of ED with respect to human health. Furthermore, the justification of DNELs in the REACH registration dossiers was given particular attention.

This substance evaluation referred to the CSRs and the IUCLID endpoint records submitted by the lead registrants for ptBP and ptAP. In addition, it also considered a number of publications and regulatory reference assessments and reports, most notably the EU RAR (EU, 2008), a RAC Opinion (RAC, 2012), and two opinions of the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK, 1981-1995; MAK, 2001).

7.9.1. Read-across considerations

In order to fulfil information requirements under REACH for the 100 – 1000 tpa tonnage level, for ptAP, registrants used data from the structurally similar ptBP where suitable and needed. In order to justify this read-across, the registrants provided a document "Read-across between p-tert-amylphenol (CAS 80-46-6) and Sodium p-tertiary amylphenol (CAS 31366-95-7) and p-tert-butylphenol (CAS 98-54-4)" (ENVIRON, 2013).

The hazard assessment of ptBP applies a read-across approach to *p*-alkylphenol ptAP on a case-by-case and endpoint-by-endpoint basis according to Annex XI of REACH. With an additional methyl group, ptAP is structurally very similar to ptBP and relevant physico-chemical properties do not differ.

In the registration of ptAP, read-across from ptBP to ptAP is used for the following endpoints/sections:

- toxicokinetics
- RDT
- reproductive toxicity (fertility only).

In contrast to the registrants, the eMSCA considered read-across between ptAP and ptBP and the possibility of using data from ptBP to fulfil information requirements for ptAP acceptable with respect to certain aspects.

Toxicokinetics

Toxicokinetics is mainly determined by physico-chemical properties such as chemical structure, molecular weight, water solubility, n-octanol/water partition coefficient and vapour pressure. As both substances have similar physico-chemical properties and as the structural difference consists only in one additional methylene group of the substituent in ortho-position when comparing ptAP to ptBP, comparable toxicokinetic behaviour of the two substances is expected.

However, the eMSCA disagreed with the registrants' statements with respect to metabolism: dealkylation, i.e. removal of the alkyl substituent is considered unlikely. Rather, glucuronidation and sulfation, as also described for other o-substituted phenols, are considered as main metabolic pathways. However, within the context of estimating absorption percentages for the oral, dermal and inhalative uptake route, this issue is of minor importance.

Repeated dose toxicity

To address RDT, a 90-day oral repeat-dose toxicity study performed with ptAP according to US EPA OPPTS 870.3100 was provided by the registrants to address concerns for both substances. Furthermore, for ptBP a two-generation reproductive toxicity study according to OECD TG 416 and a combined repeated dose and reproductive/developmental toxicity according to OECD TG 422 are available, and a developmental toxicity study performed according to EPA OPP 83-3 is available for ptAP. Systemic NOAELs derived from the three studies and the two different substances are very similar. Thus, in principle, comparable systemic effects are expected for the two different substances.

Reproductive toxicity/ED

NOAELs obtained from a two-generation reproductive toxicity study performed with ptBP, a combined repeated dose and reproductive/developmental toxicity performed with ptBP, and a developmental toxicity study performed with ptAP indicate comparable systemic toxicity. ptBP is classified as Repr. 2 for effects on fertility and sexual function. It seems plausible to the eMSCA that the effects observed in the two-generation study are linked to the endocrine activity (oestrogen/androgen/steroidogenesis (EAS)-modality) of ptBP (see Section 7.10.2.1). ptAP seems to be slightly more potent than ptBP with regard to oestrogenic activity (see Section 7.10.2.2) but the *in vivo* significance of this difference remains unclear. Nonetheless, both substances are considered by the eMSCA as reproductive toxicants inducing adverse effects on fertility and sexual function linked to the EAS modality.

Therefore, for effects on sexual function and fertility, and developmental toxicity, a similar NOAEL was assumed by the eMSCA based on the structural similarity in line with the approach used by the registrants.

Vitiligo

The registrants of ptAP did not consider skin depigmentation effects in the chemical safety assessment. However, both alkylphenols, ptBP and ptAP are known inducers of skin depigmentation, but for ptAP this effect has not yet been addressed as systematically as for ptBP in experimental studies. Reports on the occurrence of skin depigmentation in workers occupationally exposed to ptAP (Boissy and Manga, 2004; Stevenson, 1981; Stevenson, 1984) state that phenolic compounds such as ptBP and ptAP are involved in the formation of occupational vitiligo.

7.9.2. Toxicokinetics

7.9.2.1. ptBP

In *in vitro tests*, ptBP served as a substrate for tyrosinase, which hydrolysed it to *p-tert*-butylcatechol in the presence of hydrogen peroxide. The catechol species is then further metabolised to *p-tert*-butyl-1,2-benzoquinone (Jimenez and Garcia-Carmona, 1996; McGuire and Hendee, 1971; Ros et al., 1994). This may have implications on the depigmentation potential of ptBP under oxidative stress. It can be anticipated that ptBP will be conjugated and excreted as glucuronide and sulfate conjugates (Koster et al., 1981).

However, a toxicokinetic study according to OECD TG 417 is not available. Orally, ptBP was completely absorbed and excreted mainly via urine (72.9 %) and faeces (26.7 %). Intravenous administration revealed that most of the excreted dose was conjugated (glucuronidation [65-71 %] and sulfation [17-21 %]) (Freitag et al., 1982; Koster et al., 1981). Information on conjugation following oral exposure is not available, nor on metabolic differences following exposure via gavage or diet, which may distinctively affect the biological activity of the substance (Vandenberg et al., 2014). Retention of ptBP was negligible and therefore bioaccumulation is considered unlikely. There is neither an OECD dermal absorption study, nor experimental data on inhalation or dermal exposure. However, human biomonitoring studies showed that ptBP is absorbed via both routes, and metabolites are measured in the urine (Ikeda et al., 1978; Kosaka et al., 1989).

The EU RAR report (EU, 2008) contains further details on the available studies. More recent kinetic information is not available in the registration dossiers or the literature.

According to this data and considering physico-chemical properties of ptBP, such as relatively good water solubility (600 mg/L), a $\log P_{ow}$ value of 3.31 and low molecular weight (152 g/mol), an absorption of 100 % for the oral, dermal and inhalation route, respectively, was considered by the eMSCA for derivation of DNELs. With respect to dermal absorption and skin penetration in general, the physical state of the substance and its formulation has to be considered, as it is marketed primarily as solid ("white flakes").

7.9.2.2. ptAP

Experimental studies on the toxicokinetics of ptAP are not available. Based on a molecular weight of 164.24 g/mol, an experimentally determined water solubility of 193 mg/L and an experimentally determined $\log P_{ow}$ value of 3.6, high absorption via the oral, dermal and inhalation pathway can be anticipated.

This assumption is underlined by a toxicokinetic study performed with the structurally similar compound ptBP (see above).

Based on further studies performed with ptBP, 4-tert-octylphenol and nonylphenol it can be anticipated that ptAP will be conjugated and excreted as glucuronide and sulfate conjugates (Crane et al., 2008; Koster et al., 1981).

Absorption percentages of 100 % for the oral, dermal and inhalation route were taken for DNEL-derivation, respectively, by the eMSCA.

7.9.3. Acute toxicity and Corrosion/Irritation

Not considered during this substance evaluation.

7.9.4. Sensitisation

Not considered during this substance evaluation.

7.9.5. Repeated dose toxicity

7.9.5.1. Derivation of dose descriptors

During substance evaluation, the eMSCA assessed the specific concerns for nephrotoxicity, depigmentation and vitiligo, effects on female reproductive organs and effects on thyroid function.

For ptBP, RDT-studies were not available for the dermal and inhalation route. For ptAP, a RDT-study using the inhalation route was not available. In a repeated dose dermal study performed with ptAP, there were no indications of systemic toxicity (Springborn Laboratories Inc, 1992). However, there were dose-dependent local effects at the site of application. A systemic NOAEL of 25 mg/kg bw/d and a local (dermal) NOAEL of 2.5 mg/kg bw/d were derived from that study by the registrants.

The eMSCA considered this study as of no value for DNEL-derivation as vitiligo (depigmentation) considered as a sensitive endpoint of ptAP toxicity cannot be addressed by using albino rats. Further, due to the corrosive nature of the substance, only low doses could be tested which most probably precluded the assessment of systemic effects.

The relevant studies for dermal and oral RDT assessed during SEv are listed in Table 11.

Table 11

Key studies for assessment of RDT for ptBP and ptAP						
Method	**Test species**	**Test substance**	**Exposure**	**Results**	**Remarks**	**Reference /type**
EPA OPPTS 870.3100 (equivalent to OECD TG 408) Sub-chronic toxicity	Rat (Crl: CD(SD) 12 male (m)/12 females (f) per group	p-(1,1-dimethylpropyl)phenol (ptAP) Form: solid: crystalline	Oral (gavage) 90 days (Once daily) Dose groups: 0, 50, 200, 600 mg/kg bw/d Vehicle: methylcellulose	NOAEL: 50 mg/kg bw/d) based on epithelial hyperplasia of the non-glandular stomach in males, and reduced thymus weights in males and females	Read-across from ptAP to ptBP	(MPI Research Inc, 2012) Study Report
Combined RDT/reproductive toxicity screening study (OECD TG 422)	Sprague-Dawley rat (Crl:=CD, SPF); 13m/13f per group)	4-tert-butylphenol (ptBP) (99.9 %) Vehicle: 0.5 % aq. methylcellulose	Oral (gavage) approx. 6 weeks (f: 2 weeks before mating, during pregnancy until 3d day of postpartum) Dose groups: 0, 20, 60, 200 mg/kg bw	NOAEL: 60 mg/kg bw/d based on respiratory distress in exposed females, and effects on several blood parameters in males (decreased RBC and elevated WBC at 200 mg/kg bw/d)	Irritation, possibly administration artifact	(MHW, 1996)
2-Gen. reproduction toxicity study (OECD TG	Sprague-Dawley rat (Crl: CD®SD).	4-tert-butylphenol (ptBP) (99.96 %)	Oral (diet) 10 weeks	NOAEL 70 mg/kg bw/d. based on decreased		(Charles River Laboratories, 2006)

416)	F0: 28 m/28f F1: 24 m/24f	Vehicle: acetone	before mating until F1 had been weaned. Dose groups: 800, 2500, 7500 ppm (corresp. to 70, 200, and 600 mg/kg bw/d)	body weight gain, decreased weights of adrenal gland and ovaries, and vaginal atrophy from 200 mg/kg bw/d onwards		
Prenatal developmental study (EPA OPP 83-3)	Rat (Sprague-Dawley)	p-(1,1-dimethylpropyl)phenol (ptAP) Form: solid: crystalline Vehicle: corn oil	Oral gavage (a single dose daily, from gestation day 6 through gestation day 15). Dose groups: 0, 50, 200, 500 mg/kg bw/d	NOAEL: 50 mg/kg bw/d based on treatment-related clinical signs and body weight loss in maternal animals at 200 mg/kg bw/d and above.		(Springborn Laboratories Inc, 1991)

An oral subchronic gavage guideline study (MPI Research Inc, 2012) according to EPA OPPTS 870.3100 (comparable to an OECD TG 408) carried out with ptAP has been made available in 2018 as a result of the request for further studies under SEv. Results of the study were included by the registrants in dossier updates for both substances. The study was used to address the concerns identified with respect to RDT of ptBP and ptAP. This study complemented data of a combined repeated dose and reproduction/ developmental screening test (OECD TG 422) using gavage (MHW, 1996), and of a two-generation reproduction toxicity feeding study (OECD TG 416) performed with ptBP (Charles River Laboratories, 2006). The latter studies on ptBP were also used in a read-across argumentation for ptAP in order to address aspects on RDT which were considered adequate according to the eMSCA.

From a prenatal developmental toxicity study performed according to EPA OPP 83-3 (Springborn Laboratories Inc, 1991), a NOAEL of 50 mg/kg/d for systemic (maternal) toxicity was derived for ptAP and was used for the risk characterisation of both substances. This dose descriptor is in the same range as dose descriptors (NOAELs) derived from two studies performed with ptBP (i.e. OECD TG 422 study (NOAEL: 60 mg/kg bw/d based on respiratory stress and serum parameters) and the OECD TG 416 study (NOAEL: 70 mg/mg bw/d based on reduced body weight gain, decreased ovarian and adrenal weights, and vaginal atrophy)). For the oral 90-day study on ptAP made available in 2018 (MPI Research Inc, 2012), the eMSCA similarly derived a NOAEL of 50 mg/kg/d, based on epithelial hyperplasia of the nonglandular stomach in male animals as well as reduced thymus weights in male and female animals.

Conclusion

Overall, except for developmental toxicity, the need to derive adjusted DNELs which might be lower than the current ones cannot be judged (since the information needed is based on other endpoints that are not clarified, see below). An overview of the different types of DNELs which can potentially be used for risk characterisation is summarised in Section 7.9.11. It should be noted (as reported in other sections) that none of the points of departure used (and none of the calculated DNELs, respectively) consider development of (systemic) vitiligo observed in humans exposed to ptBP or ptAP. Therefore, the eMSCA concludes that a potential risk for human health remains.

7.9.5.2. Nephrotoxicity

The OECD TG 422 study on ptBP (MHW, 1996) did not report abnormalities in kidney weights or in kidney histopathology compared to controls up to a dose of 200 mg/kg bw/d (oral gavage exposure for approximately 6 weeks). However, the OECD TG 416 study performed with ptBP (Charles River Laboratories, 2006) revealed progressive nephropathy in 4/6 subchronically exposed F0 males at the highest dose level (control: 0/2 males). Animals treated at lower dose levels were not examined. 4/6 males also showed minimal but scattered hyaline droplets (Controls: 1/2 males) and 2/6 males each exhibited pigmented tubular cells, pelvic dilation, and localised glomerulonephritis. Concomitantly, the relative kidney weights of males were significantly increased in this dose group (but not in the other two dose groups). Although spontaneous nephropathy together with an altered hyaline droplet incidence and pattern is not uncommon in aged rats and a frequent observation in subchronic studies (Hard, 2008; Travlos et al., 2011), these findings may be substance-induced and toxicologically relevant. The small sample size (n=2 and n=6 in the control and the only treatment group examined) and the fact that the male rats were not particularly old at study termination and sacrifice (ca. 21 weeks) reinforce the concern.

The protein content of the hyaline droplets was not specifically determined despite an indicative Mallory-Heidenhain staining in one case (Hard, 2008). Thus, it is not clear for the eMSCA, whether the droplets typically contain the rat-specific alpha 2µ-globulin. The alpha 2µ-globulin-associated nephropathy has been described as a mechanism of carcinogenesis in the renal tubules of male rats (Swenberg and Lehman-McKeeman, 1999). Unequivocal identification of alpha 2µ-globulin is one of several hallmarks in demonstrating the species-specificity in the mode of action in renal tumorigenesis (IARC, 1999). The occurrence of hyaline droplets is associated with a variety of renal diseases, such as nephritic syndrome, IgA nephropathy, membranous glomerulonephropathy and tubulointerstitial nephritis (Yamasaki et al., 2003). In rats, lysozyme-bearing hyaline droplets are associated with histiocytic sarcoma and fibrosarcoma, whereas accumulation of albumin is observed in intraplasmic hyaline droplets in cases of chronic progressive nephropathy (de Rijk et al., 2003; Hard et al., 1993; Seely, 2014).

With respect to systemic toxicity following dermal administration it appeared that irritating and corrosive properties interfered with the testing of the systemic toxicity in the study of Springborn Laboratories Inc (1992) using ptAP. The systemic dermal NOEL is therefore derived from the worker studies in the context of depigmentation (see 7.9.6). The dose descriptor for local effects is forwarded for risk characterisation of ptAP in a read-across approach.

Conclusion

The calculation of the long-term risk of exposed workers and the general population in the registration dossiers of ptBP and ptAP is exclusively based on the skin depigmentation potential of the substance by route-to-route extrapolation for the oral route. However, based on the evaluated animal data, the eMSCA considered that nephrotoxicity might be a more sensitive endpoint with regard to chronic toxicity.

During substance evaluation, an oral (gavage) RDT study performed on ptAP according to EPA OPPTS 870.3100 on ptAP (MPI Research Inc, 2012) was made available to the eMSCA by the registrants for assessment of RDT, in particular with regard to nephrotoxicity. Concerning the kidney as a putative target organ, the study was not exonerative. Rather, minimal to mild kidney effects (e.g. cysts, calculi, chronic progressive nephropathy, hydronephrosis) were reported in high-dose males and females. Unfortunately, extended histology including Mallory-Heidenhain staining and immunohistochemical identification of alpha 2µ-globulin to clarify the species specificity of renal effects was not performed in that study.

Overall, nephrotoxicity induced by both ptBP and ptAP is an additional concern for human health which has not been considered previously. However, in view of regulatory developments that had occurred since the beginning of substance evaluation (see Sections 4.1 and 7.2), the eMSCA does not consider it proportionate to uphold a request for additional animal testing to clarify this concern.

7.9.5.3. Effects on thyroid function

The eMSCA concluded that concerns on possible effects on thyroid function have not been sufficiently clarified by the EPA OPPTS 870.3100 gavage study with ptAP (MPI Research Inc, 2012). Thyroid weight, thyroid histopathology, levels of thyroid-stimulating hormone (TSH) and the thyroid hormones triiodothyronine (T3), and thyroxine (T4) have been investigated in that study. However, the study revealed substantial variability in hormone levels within dose groups and between treatment and control groups, lacking statistical analysis to confirm normal biological variation. The eMSCA retrospectively applied inferential statistics (ANOVA, Dunnett Test, Umbrella-Williams Test) to the hormone data provided. No significant changes in hormone levels were detected. However, the T3/T4 ratio showed a dose-dependent decrease for females at termination which proved significant with all three tests. This was supported by a significant but less pronounced dose-dependent decrease already observed after four weeks. A dose-dependent T3/T4 decrease may indicate a change in T4 conversion in females. Furthermore, the TSH analysis appeared to be unreliable as there was a considerable drop of TSH between week 4 and the terminal measurement in all dose groups including the controls, implying some systematic error possibly related to sample storage/workup.

The provided study did not include data on thyroid autoantibodies (e.g. thyroglobulin antibody (anti-Tg) and thyroid peroxidase antibody (anti-TPO)) has not been performed. Furthermore, the study was performed on albino rats rather than in a non-albino rat strain. This is particularly relevant as both substances are considered inducers of vitiligo, a disorder which is strongly linked to autoimmune thyroid diseases (AITD) (see Section 7.9.6). Therefore, no conclusion on the relationship of ptBP or ptAP and AITD can be drawn based on the available animal studies.

Conclusion

Taken together, the eMSCA considers that several concerns with regard to human health remain which would need to be addressed in a specifically designed subchronic repeated dose study by oral gavage using non-albino animals. To clarify potential thyroidal effects and/or the concern related to the link between vitiligo and AITD (which has been observed in workers with occupational vitiligo that were exposed to ptBP), further examinations would be needed.

However, in view of regulatory developments that had occurred since the beginning of substance evaluation (see Sections 4.1 and 7.2), the eMSCA does not consider it proportionate to uphold a request for additional animal testing to clarify this remaining concern.

7.9.5.4. Overall conclusion

In summary, the eMSCA is of the opinion that the data to (finally and reliably) conclude on the identified concerns for human health related to nephrotoxicity and effects on thyroid function and depigmentation/vitiligo are still insufficient. Therefore, a potential risk for human health remains. In consequence, the eMSCA highly recommends refinement for the derivation of DNELs in the registrations which are anticipated to be lower than the current ones.

In spite of the remaining concerns, the main reason that the previous information requests are not further upheld is that ptBP and ptAP have in the meantime been identified as SVHC based on their ED properties for the environment following proposals submitted by the eMSCA (DE CA, 2016a; DE CA, 2016b; ECHA, 2016a; ECHA, 2016d). For ptAP, only industrial uses are still registered (see Section 7.5.2.2). Furthermore, based on the hazardous properties of ptBP, the need for a restriction has been identified by ECHA for a group of alkylphenols including these two substances (ECHA, 2021). The potential need for a restriction has also been previously explored in a RMOA conducted by the eMSCA (DE CA, 2015a; DE CA, 2015b). Hence, the eMSCA considers that the envisaged risk management measures to be initiated based on the concern for the environment may also minimise the potential risks for human health. Based on these facts, clarification of the

remaining concerns for human health by requesting further vertebrate testing is considered by the eMSCA as not proportionate and justified.

7.9.6. Vitiligo/Depigmentation

Table 12

Key studies for assessment of vitiligo for ptBP and ptAP						
Method	**Test species**	**Test substance**	**Exposure**	**Results**	**Remarks**	**Reference /type**
No specific guideline followed	Mouse (C57 black) male	4-tert-butylphenol (ptBP)	Oral (gavage) 6 months 3 times a week 0.2 M of ptBP (6 mg) Vehicle: Olive oil	LOAEL: 103 mg/kg bw/d) based on diffuse or patchy depigmentation in the majority of the animals	Used in EU-RAR	(Hara and Nakajima, 1969)
No specific guideline followed	Mouse (C57BL/6)	4-tert-butylphenol (ptBP)	Topical administration 7 months 100 µl of 1.5 M ptBP Vehicle: dissolved in DMSO/ethanol and formulated in Eucerin calming cream	LOAEL 514 mg/kg bw/d based on slight depigmentation		(Hariharan et al., 2011)
No specific guideline followed	Human/worker	4-tert-butylphenol (ptBP)	Biomonitoring study in occupationally exposed workers	Urinary levels of or below 2 mg/L ptBP was considered to protect from depigmentation	Study used to derive the German MAK value of 0.5 mg/m^3 ptBP (for more detail see MAK recommendation)	(Ikeda et al., 1978)
No specific guideline followed	Human/worker	4-tert-butylphenol (ptBP)	Biomonitoring study in occupationally exposed workers	Investigation of the relationship between external exposure and internal dosimetry of ptBP	Study used to derive the German MAK value of 0.5 mg/m^3 ptBP (for more detail see MAK recommendation)	(Kosaka et al., 1989)

Being a widely recognised occupational disease, studies on worker cohorts and case studies demonstrated that ptBP is an inducer of chemical vitiligo. There is a remarkably large range in the manifestation period of depigmentation, from several months up to several years of ptBP exposure. Unfortunately, most studies lacked ambient or biological measurements to estimate exposure concentrations/doses. Hence, it is difficult to determine protective dose levels and to conclude on the most important exposure route (which in turn would shed a better light on the most relevant physical state of the substance with regard to penetration and absorption). In workers occupationally exposed to ptAP, the occurrence of vitiligo has been described as well (Harris, 2017; Kahn, 1970; Stevenson, 1981; Stevenson, 1984). Boissy and Manga (2004) state in a review report that phenolic compounds such as ptBP and ptAP are involved in the formation of occupational vitiligo. The association between vitiligo and ptAP does not appear to have been studied as systematically as for ptBP (Stevenson, 1981; Stevenson, 1984).

The German MAK Commission (MAK, 1981-1995) derived a national occupational exposure limit for ptBP, i.e. a MAK value of 0.5 mg/m^3 (MAK = maximum concentration at the workplace) and a biological tolerance value (BAT) of 2 mg/L urine, taking into account the biomonitoring studies of Ikeda et al. (1978)) and Kosaka et al. (1989)). It should be mentioned that the sample population of the Ikeda study was fairly small (n≤9). In its supporting documentation, the MAK Commission discussed several limitations and uncertainties of the proposed OEL of 0.5 mg/m^3 that are mainly associated with the very limited database, the unknown (and presumably high) extent of dermal exposure, and a reverse calculation of urinary excretion rates to air exposure levels relying on too many assumptions. Nevertheless, the MAK and the BAT value appear to be sufficiently effective in protecting from ptBP-induced vitiligo. In fact, since the enforcement of these limit values new cases of occupational vitiligo were not recorded in Germany. A number of EU member states have adopted the MAK value thus becoming a mutually accepted OEL.

In comparison to the available human evidence, animal studies investigating the depigmentation-inducing activity of ptBP and ptAP are surprisingly scarce. With one exception, only older studies, often as summaries only and/or lacking testing details, are available. This data confirm that ptBP causes patchy depigmentation both by dermal and oral exposure (and possibly also by inhalation, although information on this route is very poor), thus demonstrating that the depigmentation can be induced by local contact but also systemically after absorption. However, the vehicle, the type of formulation and administration, may have an impact on the severity and time point of first occurrence with regard to skin effects.

Taken together, the following dose descriptors are proposed and used for provisional risk characterisation by the eMSCA:

<u>Systemic, oral route</u>: LOAEL = 103 mg/kg bw/d (based on skin depigmentation in black mice (Hara and Nakajima, 1969).

<u>Systemic, inhalation and dermal route</u>: MAK = 0.5 mg/m^3 and BAT = 2 mg/l urine (based on human information on depigmentation protection, urinalysis and ambient air analysis from Ikeda et al. (1978) and (Kosaka et al., 1989).

<u>Local, dermal route:</u> LOAEL = 514 mg/kg/d (based on topical induction of depigmentation in wild mice, as reported by (Hariharan et al., 2011).

Idiopathic vitiligo and chemically induced depigmentation share many features that make them indistinguishable (Harris, 2017). Both mechanistic research and clinical findings should be taken into consideration for the identification of potential health hazards for known depigmentation-triggering substances such as ptBP or ptAP.

According to the so-called convergence theory, vitiligo is suspected to originate from a combination of aetiological factors that impact melanocyte viability, including oxidative stress, auto-immune T-cell hyper-reactivity, and genetic predisposing mutations (Kundu et al., 2018). Whereas formation of reactive oxygen species (ROS) and a genetically related inability to cope with oxidative stress are deemed responsible for the onset of the disorder,

a triggered autoimmune process is suspected to be involved in the spread of depigmentation beyond the areas of contact (Boissy and Manga, 2004; Kroon et al., 2013; Lotti and D'Erme, 2014).

Occupational vitiligo caused by chemical inducers may take a chronic course. There might be differences in the mode of action of ptBP or ptAP and hydroquinone, the latter being a well-known chemical for its depigmentation properties. Due to their structural similarity to the melanin precursor tyrosine, it has been postulated that alkylphenols and hydroquinone compete with tyrosine for the active site of tyrosinase, thus interfering with melanin synthesis but also leading to the catalytic formation of cytotoxic semiquinone radicals initiating apoptotic cell death through membrane lipid peroxidation. However, experimental evidence discarded a direct involvement of tyrosinase activity in vitiligo melanocytes induced by ptBP in favour of tyrosinase-related protein-1, another melanocyte-specific enzyme, which appears to be responsible for the catalytic conversion of phenols and generation of destructive ROS (Boissy and Manga, 2004). In addition, the pathophysiological responses significantly differ between hydroquinone and ptBP: whereas the former induces necrosis, the latter activates the apoptotic death pathway in melanocytes, thus also recruiting distinct immunological mechanisms (Hariharan et al., 2010).

Recent experimental findings linked the oxidative stress response by phenols to the autoimmune function in melanocyte apoptosis and identified a number of key molecules involved (Toosi et al., 2012). Accordingly, sensitive melanocytes accumulate misfolded proteins in the endoplasmic reticulum as a response to ptBP-elicited redox disruption. This leads to the activation of the unfolded protein response, in particular the up-regulation of the transcription factor X-box-binding protein 1 (XBP1). Polymorphism in the XBP1 gene may at least partially explain the genetic predisposition of vitiligo (Passeron and Ortonne, 2012). More important here, the transcription factor activates the production of the two immune mediating cytokines interleukin-6 and -8. Hence, not only surrounding epidermal cells but melanocytes themselves initiate a chemical-triggered immune response by releasing these cytokines and thus target these cells for their removal even beyond the area of chemical contact and thus promote the autoimmune spread of vitiligo.

The autoimmune response is cell-mediated. This was demonstrated *in vitro* and *in vivo* by activation of dendritic cell-mediated killing of damaged melanocytes following ptBP exposure (Kroll et al., 2005) as well as by the activation of cytotoxic T-cells (Lili et al., 2012) and reduction of regulatory T-cells (Klarquist et al., 2010) in perilesional epidermis in vitiligo patients.

The autoimmune response is distinct from sensitisation. For the former, it is not the chemical itself acting as a hapten for antigen presentation. Rather, apoptotic cell debris is the ultimate inducer of cell-mediated autoimmunity. The autoimmune mechanism might explain the autonomous spreading of skin depigmentation but also the observed damage of internal organs (esp. liver, spleen, thyroid) of exposed workers (inhalative and dermal).

The systemic manifestation of vitiligo and an association between (idiopathic) vitiligo and autoimmune thyroid disease (AITD) has been well documented (Baldini et al., 2017; Hegedüs et al., 1994; Kroon et al., 2013; Liu et al., 2016a; Liu et al., 2016b; Lotti and D'Erme, 2014; Patel et al., 2017). A meta-analysis showed that in patients affected by vitiligo, the prevalence of AITD was 14.3 %, while positivity to thyroid-specific antibodies (i.e., anti- Tg, anti-TPO, and anti-TSH receptor (anti-TSHR)) was found in 20.8 % of them. Moreover, the presence of anti-thyroid antibodies in the serum of patients affected by vitiligo was detected in 77 out of 79 vitiligo patients analysed, suggesting a possible pathogenetic role. Vice versa, the prevalence of vitiligo among AITD patients has been reported to vary from 2.7 to 7 % (Baldini et al., 2017). Prevalence of AITD in juvenile and adolescent vitiligo patients appears to be particularly high, and calls have been made for thyroid function tests and antibody screening in all paediatric patients with non-segmental vitiligo (Kroon et al., 2013).

Shared susceptibility genes that predispose to vitiligo and the two major AITDs, Hashimoto's and Graves' disease have been identified (Spritz, 2010). Moreover, evidence amounts that melanocyte antigens are specifically expressed in the thyroid of Hashimoto

patients (Spritz et al., 2004). On the other hand, melanocytes also express thyroid-specific antigens (Slominski et al., 2002). These findings may be key to the understanding of molecular mechanisms for the observed co-occurrence of AITD and vitiligo.

However, it is not clear, whether ptBP and ptAP may trigger these disorders. The available animal depigmentation studies (using non-albino strains) did not study thyroid function or thyroid autoantibodies. There is only one report that investigated the presence of thyroid autoantibodies in workers exposed to ptBP and who developed both, vitiligo and goitre (Ebner et al., 1979). Likewise, the evidence for endocrine activity with regard to the thyroid (T)-modality of ptBP is poor (see chapter 7.10.2) and restricted *in vivo* to standard parameters determined in albino rats.

The systemic nature of ptBP- or ptAP-induced vitiligo may give rise to concerns towards pathological manifestations beyond skin depigmentation. Melanocytes as the principal target cells are not only located in the epidermis and hair follicles but also in other tissues, such as mucosa, cochlea of the ear, iris of the eye, and the mesencephalon of the brain (Yamaguchi and Hearing, 2014). In the ear, melanocytes are located in the *stria vascularis* where they control the ion homeostasis for creating the endocochlear electrical potential. The electrical activity of ciliary cells in the labyrinth is closely connected with their physiological ability to send afferent information to brain areas involved in auditory and balance functions. In the eye, melanocytes are found in the retinal pigment epithelium and the uveal tract. Melanocytes present in the choroid are responsible for constitutive eye pigmentation and protection against ultraviolet (UV) radiation. These cells are important for the degradation of toxic factors (Ciescinska et al., 2016). A disturbed sensory function due to chemically induced depigmentation and melanocyte destruction, respectively, is a realistic consequence of chronic systemic exposure, if the substance reaches these target tissues.

Therefore, it is conceivable to hypothesise that chemically-induced melanocyte destruction may affect sensory organs which are not routinely examined in the context of chemically induced depigmentation vitiligo in humans. Furthermore, histopathological changes in the inner ear or the eye may occur, **even before skin depigmentation becomes manifest, initiating auditory and visual disorders which develop over time**. Clinical history reports revealed that a number of ocular and auditory findings co-exist in (idiopathic) vitiligo patients (Aydin et al., 2018; Ciescinska et al., 2016; Karadag et al., 2016; Moghaddam et al., 2018). Wagoner et al. (1983) reported that 60/223 patients with vitiligo (26.9 %) had retinal pigment epithelium hypopigmentation or atrophy, whereas in 69/223 vitiligo patients (30.9 %) evidence for old chorioretinal scars was present. Anbar et al. (2015) observed in 64 inner ears of 53 vitiligo patients (60 %) cochlear dysfunction using distortion product otoacoustic emissions. A rare form of vitiligo such as the Vogt-Koyanagi-Harada syndrome affects the hair, eye, inner ear, and brain (Rodrigues et al., 2017). This syndrome is also suspected to have an auto-immune aetiology (Greco et al., 2013). Regarding vitiligo-related concerns, not only any skin depigmentation should be recorded but also any histopathological changes in the eye and the ear, including melanocyte destruction/apoptosis.

Conclusion

Evidence from animal studies regarding the skin depigmentation potential of bioavailable ptBP or ptAP is scarce. However, there is sufficient evidence from human data indicating that ptBP and ptAP are inducers of occupational vitiligo. The EPA OPPTS 870.3100 gavage study with ptAP that was provided in order to fulfil the eMSCA request for information within the SEv process was unable to inform on depigmentation and melanocyte destruction. This was a result of the test being carried out with albino rats. Therefore, it could not be clarified whether depigmentation could manifest earlier or at lower levels in melanocyte containing tissues other than skin (e.g. eye).

In view of the developments described in Sections 4.1 and 7.2, the eMSCA is of the opinion that there is no justification to uphold the request for additional animal testing.

7.9.7. Mutagenicity

Not considered during this substance evaluation.

7.9.8. Carcinogenicity

Not considered during this substance evaluation.

7.9.9. Toxicity to reproduction (effects on sexual function and fertility, and developmental toxicity)

7.9.9.1. ptBP

Using the information of the two-generation reproduction toxicity study according to OECD TG 416 (Charles River Laboratories, 2006), a NOAEL of 70 mg/kg bw/d was derived in the EU-RAR (EU, 2008) for effects on sexual function and fertility based on decreased ovarian weight in P0 and F1 females, and increased vaginal epithelial atrophy in P0 females in the mid and high dose. The eMSCA concurs with this NOAEL. For developmental effects in the EU-RAR, a NOAEL of 70 mg/kg bw/d was derived based on reduced pup and litter weight in F1 and F2 from LD 14 at and beyond 2500 ppm. According to REACH information requirements, developmental toxicity is a standard information in the respective tonnage band (> 1000 tpa) and cannot be replaced by a two-generation developmental study, as important developmental parameters are not tested in the OECD TG 416 study. Accordingly, there was an information gap for this endpoint for ptBP. Considering the OECD TG 422 screening results, a NOAEL of ≥ 200 mg/kg bw/d was derived for both, embryo-toxicity and teratogenicity. However, the study design is not appropriate to address developmental toxicity reliably and fully. A NOAEL of 50 mg/kg bw/d was derived by the eMSCA for ptAP in a more robust EPA OPP 83-3 prenatal developmental toxicity study (comparable to OECD TG 414) (Springborn Laboratories Inc, 1991) .

As per Commission Regulation (EU) No. 605/2014, ptBP has been classified as Repr. 2, H361f (suspected of damaging fertility) according to CLP criteria. This classification is based on a CLH proposal and corresponding RAC opinion (RAC, 2012) highlighting decreased number of implantation sites and live pups born as well as slightly smaller litter size compared to controls. Though it was acknowledged that during specific time periods, exposure concentration exceeded the limit dose for classification of 1000 mg/kg bw/d, RAC pointed out that the limit dose was exceeded only during lactation. Furthermore, it was stated that the limit dose is a guidance value for testing and that there is no actual limit value for CLP classification.

Regarding developmental toxicity, RAC concluded that the available data was not sufficient to propose classification, because of the absence of embryo-toxicity and teratogenicity in the OECD TG 422 study and due to the fact that the doses causing significant fertility effects in the OECD TG 416 study did not cause significant developmental toxicity effects that would support classification.

A prenatal development study according to OECD TG 414 (first species) is a standard testing requirement according to REACH Regulation, Annex X. This information was not provided in the registration. The CSR waived this test based on a read-across justification to a prenatal OECD TG 414 study available for nonylphenol (IBR Forschungs GmbH, 1992) in which no embryo-toxic or teratogenic effects were observed. However, the eMSCA does not accept this read-across approach for a less related substance with a negative outcome. Furthermore, a prenatal study according to EPA OPP 83-3 testing the more closely related analogue ptAP (Springborn Laboratories Inc, 1991) found statistically significant embryo-toxic effects at the highest dose tested (500 mg/kg bw/d). Signs of maternal toxicity were observed already at 50 mg/kg.

The OECD TG 416 study with ptBP also reported some developmental effects: a decrease in pup and litter weight in F1 and F2 at 2500 ppm and a smaller litter size at 7500 ppm. At this dose level, a decrease in pup survival and a delay in vaginal opening and preputial

separation were also found in F1 only. Maternal body weight effects at the top dose level may have confounded these results, although the differences in food consumption and body weight were not severe during gestation through lactation (-15.6 % lower body weight in the high dose compared to controls at the end of gestation and at start of lactation, respectively). Besides that, an OECD TG 416 study does not cover all endpoints of a prenatal study following OECD TG 414. For instance, visceral and skeletal defects are not or only insufficiently recorded.

The eMSCA concluded that the initially available information on developmental toxicity of ptBP presented in the CSR was insufficient. Waiving this endpoint on the basis of negative studies with the distantly related nonylphenol was considered inappropriate. Instead an EPA OPP 83-3 study revealing an (non-significant but dose-dependent) increase in skeletal variation by the close structural analogue ptAP (Springborn Laboratories Inc, 1991) is considered sufficient by the eMSCA to investigate developmental toxicity for the purpose of this substance evaluation. Based on the results of this study and read-across from ptAP, for both substances, the eMSCA concludes that there is currently no indication of developmental toxicity effects relevant for classification.

7.9.9.2. ptAP

Fertility data based on tests performed with ptAP are not available. In order to fulfil REACH information requirements, the registration contains results from a two-generation reproductive toxicity study according to OECD TG 416 (Charles River Laboratories, 2006), and a combined repeated dose and reproductive/developmental toxicity study according to OECD TG 422 (MHW, 1996) performed with the structurally similar substance ptBP along with a read-across justification. The eMSCA considered read-across between the two substances acceptable for the endpoint fertility. Therefore, ptAP might also warrant classification as Repr. 2, H361f (suspected of damaging fertility) according to the CLP criteria. From the two-generation reproductive toxicity study, a NOAEL of 70 mg/kg bw/d was derived for systemic and fertility effects. From the combined repeated dose and reproductive/developmental toxicity studies, a systemic NOAEL of 60 mg/kg bw/d and a NOAEL for fertility of 200 mg/kg bw/d were derived. Thus, the eMSCA considers 70 mg/kg bw/d as NOAEL for fertility effects of ptAP.

The developmental toxicity of ptAP was investigated in a study performed according to EPA OPP 83-3 (Springborn Laboratories Inc, 1991). The eMSCA considers this study equivalent to OECD TG 414. From this study, a systemic NOAEL of 50 mg/kg bw and a developmental NOAEL of 200 mg/kg bw/d were derived.

In summary, the eMSCA concludes that the available information is sufficient to conclude on reproductive toxicity of ptAP and there is currently no indication of developmental toxicity effects relevant for classification.

7.9.10. Hazard assessment of physico-chemical properties

Not relevant for substance evaluation.

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

7.9.11.1 Workers

The following DNELs were derived by the eMSCA.

Table 13

CRITICAL DNELS/DMELS FOR WORKERS				
Endpoint of concern	**Critical study(ies)**	**Corrected dose descriptor(s)**	**DNEL/ DMEL**	**Justification/ Remarks**

		(e.g. NOAEL, NOAEC)		
Inhalation, long-term systemic for ptBP and ptAP	Two-generation reproductive toxicity study in rat with ptBP	NOAEC(corr.) 123 mg/m³	DNEL 4.9 mg/m³	AF for duration of exposure: 2 (default, subchronic to chronic) AF remaining interspecies differences: 2.5 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:25
Inhalation, long-term systemic for ptBP and ptAP	Prenatal developmental toxicity study in rat with ptAP	NOAEC(corr.) 88 mg/m³	DNEL 1.2 mg/m³	AF for duration of exposure: 6 (default, subchronic to chronic) AF remaining interspecies differences: 2.5 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:75
Inhalation, long-term systemic for ptBP and ptAP	90 d Oral toxicity study in rat with ptAP	NOAEC(corr.) 88 mg/m³	DNEL 3.5 mg/m³	AF for duration of exposure: 2 (default, subchronic to chronic) AF remaining interspecies differences: 2.5 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:25
Dermal, long-term systemic for ptBP and ptAP	Dermal subchronic toxicity study in rat	NOAEL 25 mg/kg/d	DNEL 0.25 mg/kg/d	AF for duration of exposure: 2 (default, subchronic to chronic) AF remaining interspecies differences: 10 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:100
Dermal, long-term systemic for ptBP and ptAP	Prenatal developmental toxicity study in rat	NOAEL 50 mg/kg/d	DNEL 0.16 mg/kg/d	AF for duration of exposure: 6 (default, subchronic to chronic) AF remaining interspecies differences: 10 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:300
Dermal, long-term systemic for ptBP	90 d oral toxicity study in rat with ptAP	NOAEL 50 mg/kg/d	DNEL 0.5 mg/kg/d	AF for duration of exposure: 2 (default, subchronic to chronic) AF remaining interspecies differences: 10 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:100

Dermal, long-term local for ptBP and ptAP	Dermal subchronic toxicity study in rat	NOAEL 2.5 mg/kg/d	DNEL 0.5 mg/kg/d	AF for duration of exposure: 1 (default, subchronic to chronic) AF remaining interspecies differences: 1 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:5
Calculation as dermal dose	Dermal subchronic toxicity study in rat	NOAEL 17.2 µg/cm²	DNEL 3.4 µg/cm²	AF for duration of exposure: 1 (default, subchronic to chronic) AF remaining interspecies differences: 1 (default) AF for intraspecies differences: 5 (default, worker) Overall AF:5

An overview of the different types of DNELs that can be potentially used for risk characterisation is summarised in Table 13. However, it should be noted that none of the used point of departures (and none of the calculated DNELs, respectively) considers development of (systemic) vitiligo observed in humans exposed to ptBP or ptAP. Available animal studies addressing depigmentation effects of ptBP by various routes of exposure (EU, 2008) are lacking specific details and therefore are not usable for quantitative risk assessment in the context of the REACH regulation. In addition, no systemic effects were observed in the subchronic dermal toxicity study with the read-across substance ptAP (Springborn Laboratories Inc, 1992). However, because the corrosive properties of ptAP interfered with testing, the test is deemed inappropriate for assessment of long-term systemic toxicity via skin contact. The endpoint of chemically-induced vitiligo and the relationship between external and internal ptBP exposure has been addressed in two biomonitoring studies in workers occupationally exposed to ptBP (Ikeda et al. (1978) and Kosaka et al. (1989), see Section 7.9.5). Based on these studies, an OEL for inhalation exposures to ptBP has been established in Germany. The eMSCA considers the use of the ptBP biomonitoring data as an appropriate base for setting a long-term inhalation DNEL that should protect against visible skin depigmentation associated with exposure to ptBP.

Table 14

Hazard conclusions for workers for ptBP and ptAP			
Route	**Type of effect**	**Hazard conclusion**	**Most sensitive endpoint**
Inhalation	Systemic effects – long term	OEL = 0.5 mg/m^3	Skin depigmentation in workers exposed occupationally ptBP
Dermal	Systemic effects – long term	DNEL = 0.07 mg/kg bw/d	Skin depigmentation in workers exposed occupationally to ptBP

7.9.11.2 Consumer

The table below contains the DNELs derived by the eMSCA for consumers.

Table 15

CRITICAL DNELS/DMELS FOR CONSUMERS				
Endpoint of concern	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Inhalation, long-term systemic for ptBP	Two-generation reproductive toxicity study in rat with ptBP	NOAEC(corr.) 60.87 mg/m³	DNEL 1.2 mg/m³	AF for duration of exposure: 2 (default, subchronic to chronic) AF remaining interspecies differences: 2.5 (default) AF for intraspecies differences: 10 (default, general population) Overall AF:50
Inhalation, long-term systemic for ptBP and ptAP	Prenatal developmental toxicity study in rat with ptAP	NOAEC(corr.) 43.5 mg/m³	DNEL 0.29 mg/m³	AF for duration of exposure: 6 (default, subchronic to chronic) AF remaining interspecies differences: 2.5 (default) AF for intraspecies differences: 10 (default, general population) Overall AF:150
Inhalation, long-term systemic for ptAP	Oral toxicity study in rat with ptAP	NOAEC(corr.) 43.5 mg/m³	DNEL 0.87 mg/m³	AF for duration of exposure: 2 (default, subchronic to chronic) AF remaining interspecies differences: 2.5 (default) AF for intraspecies differences: 10 (default, general population) Overall AF:50
Dermal, long-term systemic for ptBP and ptAP	Dermal subchronic toxicity study in rat	NOAEL 25 mg/kg/d	DNEL 0.125 mg/kg/d	AF for duration of exposure: 2 (default, subchronic to chronic) AF remaining interspecies differences: 10 (default) AF for intraspecies differences: 10 (default, general population) Overall AF:200
Dermal, long-term systemic for ptBP and ptAP	Prenatal developmental toxicity study in rat	NOAEL 50 mg/kg/d	DNEL 0.0833 mg/kg/d	AF for duration of exposure: 6 (default, subchronic to chronic) AF remaining interspecies differences: 10 (default) AF for intraspecies differences: 10 (default, worker) Overall AF:600
Dermal, long-term local for ptBP and ptAP	Dermal subchronic toxicity study in rat	NOAEL 2.5 mg/kg/d	DNEL 0.25 mg/kg/d	AF for duration of exposure: 1 (default, subchronic to chronic) AF remaining interspecies differences: 1 (default) AF for intraspecies differences: 10 (default, general population) Overall AF:10

Calculation as dermal dose	Dermal subchronic toxicity study in rat	NOAEL 17.2 µg/cem²	DNEL 1.72 µg/cm²	AF for duration of exposure: 1 (default, subchronic to chronic) AF remaining interspecies differences: 1 (default) AF for intraspecies differences: 10 (default, general population) Overall AF:10

The eMSCA is of the opinion that long-term DNELs are also protective for exposures of shorter duration. When using the current German OEL of 0.5 mg/m^3 (AGW; TRGS 900) for DNEL calculation, following long-term systemic inhalation and dermal DNELs are obtained which are also considered to be protective for exposures of shorter duration.

Table 16

Hazard conclusions for consumers for ptBP and ptAP			
Route	**Type of effect**	**Hazard conclusion**	**Most sensitive endpoint**
Inhalation	Systemic effects – long term	OEL = 0.03 mg/m^3	Skin depigmentation in workers exposed occupationally to the read-across substance ptBP
Dermal	Systemic effects – long term	DNEL = 0.004 mg/kg bw/d	Skin depigmentation in workers exposed occupationally to the read-across substance ptBP

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

As pointed out in Section 7.9.9.2, the eMSCA is of the opinion that ptAP, based on read-across to ptBP, might also be classified as Repr. 2, H361f (suspected of damaging fertility) according to CLP criteria. Furthermore, both ptBP and ptAP might fulfil the criteria as an ED for human health (see Sections 7.10.2.1 and 7.10.2.2) according to the WHO definition and the amended CLP Regulation.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

During substance evaluation, the concern for ptBP and ptAP being ED for the environment was assessed leading in 2016 to identification of both substances as SVHC due to their ED properties for the environment (Article 57f). For details, please refer to the respective Annex XV SVHC dossiers for ptBP and ptAP and the MSC opinions (see 4.1.2. for references and links). Based on the criteria of the new CLP hazard classes, the eMSCA considers ptBP and ptAP as likely to fulfil the criteria for harmonised classification as ED Cat.1 for the environment.

Based on the assessment of the eMSCA, ptBP and ptAP meet the definition/criteria of an ED according to the World Health Organisation/IPCS definition as well as according to the new CLP criteria for EDs. There is scientific evidence from good quality studies that both substances cause endocrine mediated adverse effects in several fish species.

- *In vitro* data unambiguously show that ptBP and ptAP act as ligand of fish (as well as mammalian) oestrogen receptors. Modulation of ER-mediated gene expression by ptBP/ptAP was observed on transcriptional, protein and cell-physiological levels.

- *In vivo* data substantiate the endocrine mode of action. Endpoints indicative for an oestrogenic mode of action were affected in all fish species tested (three species for ptBP and six species for ptAP). Effects observed included vitellogenin (VTG) induction, feminisation of gonadal ducts and other histological alterations and reduced male secondary sex characteristics.
- A sex ratio biased towards females was observed in fish species (in one species for ptBP, in five species for ptAP). This endpoint is diagnostic for both an endocrine mode of action and an adverse effect.
- Other observed adverse effects (reduced reproduction, reduced growth) in fish are plausibly linked to an oestrogenic mode of action. But other modes of action cannot be entirely ruled out. Data show no evidence that the observed adverse effects are caused by systemic toxicity.

The ED properties are supported by read-across from other alkylphenols (4-nonylphenol and 4-tert-octylphenol).

Thus in summary, the endocrine mediated effects observed in fish after exposure to ptBP or ptAP, respectively, are considered to have the potential to adversely affect population stability and recruitment. These adverse effects not only persist after cease of exposure but also occur after transient short-term exposure at sensitive live stages. They thus may adversely affect populations in the longer-term and migratory species not only locally but also in regions where no exposure occurred. Apart from mammals (see Section 7.10.2), no reliable information is available for ptBP and ptAP about whether these substances can cause ED-related adverse effects on taxa other than fish (e.g. amphibians or even in invertebrates). Based on current data and knowledge, a safe level of exposure is difficult to derive although it may exist.

Consequently, it has been agreed at EU level that both substances fulfil the WHO/IPCS criteria for an ED in the environment. Furthermore, in accordance with the recently established CLP criteria for ED, the eMSCA considers that both substances can be classified as ED ENV Cat. 1.

7.10.2. Endocrine disruption - Human health

7.10.2.1. ptBP

EAS-modality

In vitro binding tests of ptBP demonstrated weak affinity to oestrogen receptors (ER) (Akahori et al., 2005; Akahori et al., 2008; Blair et al., 2000; Kuiper et al., 1998; Olsen et al., 2005; Olsen et al., 2002; Yamasaki et al., 2004). Accordingly, transactivational reporter gene assays, and proliferation assays (E-screen) showed weak agonist activity (Kolle et al., 2010; Körner et al., 1998; Kuiper et al., 1998; Olsen et al., 2005; Olsen et al., 2002; Routledge and Sumpter, 1997; Soto et al., 1995a; Soto et al., 1995b) as well as some indication for antagonist activity (Kolle et al., 2010). The substance was also shown *in vitro* to induce several oestrogen-regulated proteins at concentrations in the micromolar range (Olsen et al., 2002). In line with these published *in vitro* data, the ToxCast ER model shows weak oestrogenic activity with a score of 0.161 but no anti-oestrogenic activity (score: 0.00).[7] *In vivo*, ptBP displayed oestrogenic as well anti-oestrogenic activity in uterotrophic assays (equivalent to OECD TG 440) with immature rats (subcutaneous injection) (Akahori et al., 2008; Yamasaki et al., 2004). With regard to the androgen receptor (AR), one study reported anti-androgenic but no androgenic activity in a reporter gene assay without providing information on potency (Kolle et al., 2010). On the other hand, the ToxCast AR model showed neither androgenic nor anti-androgenic

[7] https://comptox.epa.gov/dashboard/chemical/bioactivity-toxcast-models/DTXSID1020221

activity[7]. Furthermore, some evidence exists from cell culture experiments and mechanistic *in vivo* studies that ptBP may interfere with steroidogenesis (Haavisto et al., 2003; Myllymaki et al., 2005).

With regard to higher tier *in vivo* studies, a combined RDT/reproduction toxicity screening study (MHW, 1996), and a two-generation reproductive toxicity study (Charles River Laboratories, 2006) are available for ptBP. In the RDT/reproductive toxicity screening study, effects on EAS-mediated/sensitive parameters were not observed up to a dose of 200 mg/kg bw/d. On the other hand, in the two-generation study, testing ptBP up to 600 mg/kg bw/d (nominal), several parameters related to fertility and sexual function which are mediated by or are sensitive to the EAS-modality were affected. Effects included atrophy of the vaginal epithelium (high dose in P0, mid and high dose in F1), reduced ovary weight (mid and high dose in P0, high dose in F1), reduced pituitary weight (both generations; high dose females) lower number of growing follicles (high dose F1), irregular oestrous cycle (high dose P0), reduced implantation sites (high dose in both generations), and slightly lower litter size (high dose in both generations). The specificity of the observed effects was challenged by substantial body weight effects in the high dose, particularly in the F1 females (> -20 % lower body weight compared to controls). Nonetheless, the effects on fertility and sexual function were considered sufficiently specific by RAC to classify ptBP as Repr. 2. It seems plausible by the eMSCA that the effects on the above-mentioned EAS-mediated/sensitive parameters are due to the endocrine (namely oestrogenic/anti-oestrogenic and steroidogenic) activity of ptBP. Therefore, ptBP might fulfil the definition of an ED for human health according to the WHO-definition as well as the newly adopted CLP criteria.

T-modality

With respect to a thyroid-related activity of ptBP, dual health concerns have to be considered: the substance may interfere with the thyroid hormone system in a "classical" way (e.g. by interfering with production, release, distribution, uptake, metabolism, or action of thyroid hormones). On the other hand, ptBP may affect thyroid function based on a mechanism linking AITD to depigmentation (see Section 7.9.6). In any case, the rather limited data do not allow to draw a final conclusion on the thyroid effects of ptBP. *In vitro* studies with ptBP did not provide evidence for competitive binding to transthyretin (Van Den Berg et al., 1991), interaction with thyroid hormone-receptors (TR) (Kitagawa et al., 2003; Paul-Friedman et al., 2019), or inhibition of iodothyronine deiodinases (DIO 1, 2, and 3) (Olker et al., 2019) and iodotyrosine deiodinase (also known as dehalogenase) (Olker et al., 2021). ptBP was ambiguous as an inhibitor for TPO (less than 50% efficacy) (Paul Friedman et al. (2016), see also the CompTox dashboard[8]). *In vivo*, the OECD TG 416 study did not find changes in the thyroid weight in any generation but thyroid histology and hormone measurements were not performed. Increases in liver weight and decreases in pituitary and brain weights were observed but these are not specific for thyroid-related effects.

In 2018, a 90-day oral gavage guideline study (according to US EPA OPPTS 870.3100) became available which tested ptAP in rats (MPI Research Inc, 2012). According to the authors, treatment-related findings on thyroid weight, thyroid histopathology and hormone levels (T3, T4, TSH) were not seen. However, a dose-dependent decrease in the T3/T4 ratio was observed, and there seemed to be issues with the TSH measurement (see also 7.9.5.3). Considering the nosologic triad of vitiligo, goiter and hepatosplenopathy observed in workers exposed to ptBP (see 7.9.6), the oral gavage study with ptAP (MPI Research Inc, 2012) did not report significant effects on liver or spleen but observed mild hepatodiaphragmatic nodule and minimal mononuclear cell infiltration in the liver. Most importantly, none of the studies performed with either ptBP or ptAP utilised non-albino rats, and investigated vitiligo and the occurrence of thyroid autoantibodies which could

[8] https://comptox.epa.gov/dashboard-viztool//plot?representative_sample=true&url_env=https://comptox.epa.gov/dashboard-api/&assay_endpoint_nm=CCTE_Simmons_AUR_TPO_dn&dsstox_id=DTXSID1020221

have further informed on putative autoimmune thyroid effects. Therefore, ptBP is considered inconclusive with respect to the T-modality in particular related to AITD.

In conclusion, in view of the developments described under 4.1 and 7.2, the eMSCA is of the opinion that it is not justified to uphold the requirement for additional animal testing.

7.10.2.2. ptAP

EAS-modality

Similarly to ptBP, binding tests indicate weak competitive binding of ptAP to ERs (Akahori et al., 2005; Akahori et al., 2008; Blair et al., 2000; Kuiper et al., 1998) and agonist activity in transactivational reporter gene assays, and proliferation assays (Routledge and Sumpter, 1997; Soto et al., 1995b). *In vivo*, ptAP - similar to ptBP - displayed oestrogenic as well anti-oestrogenic activity in uterotrophic assays (equivalent to OECD TG 440) with immature rats (subcutaneous injection) (Akahori et al., 2008; Yamasaki et al., 2003). These published findings are in concordance with the ToxCast ER model showing weak oestrogenic (score: 0.282) as well as anti-oestrogenic activity (score: $1.92*10^{-4}$)[9]. To the best of the eMSCA's knowledge, studies with regard to interaction with the AR are not available for ptAP. The ToxCast AR model did not show androgenic or anti-androgenic activity[9]. This is in line with an *in vivo* Hershberger assay, reporting absence of androgenic or anti-androgenic activity for ptAP (Yamasaki et al., 2003). An RDT study (MPI Research Inc, 2012; Springborn Laboratories Inc, 1992) and a prenatal developmental toxicity study with ptAP according to OECD TG 414 (Springborn Laboratories Inc, 1991) did not show effects on EAS-mediated/sensitive parameters. However, these studies are limited with regard to the EAS-modality and dedicated higher tier *in vivo* studies investigating effects on fertility and sexual function are not available for ptAP. As read-across is considered acceptable by the eMSCA, the findings from the two-generation study with ptBP (Charles River Laboratories, 2006) imply that ptAP similarly affects EAS-mediated/sensitive parameters related to fertility and sexual function. With regard to endocrine activity, the available *in vitro* studies suggest a slightly higher oestrogenic potency (1.4 – 7 fold higher) based on ER binding (Akahori et al., 2005; Blair et al., 2000), reporter gene activation (Routledge and Sumpter, 1997), proliferative response in the E-screen (Soto et al., 1995b), and in the ToxCast ER model (scores: 0.161 and 0.282 for ptBP and ptAP, respectively). Data are insufficient to compare the potencies of ptAP and ptBP *in vivo*. In uterotrophic assays, both chemicals were tested in different dose-ranges (ptBP in Yamasaki et al. (2004): 0, 100, 300, and 1000 mg/kg bw/d; lowest effective dose: 100 mg/kg bw/d; ptAP in Yamasaki et al. (2003): 0, 8, 40, and 200 mg/kg bw/d; lowest effective dose: 200 mg/kg bw/d). Interestingly, a study from the 1930s reported a higher oestrogenic potency of ptAP (80 % positive) compared to ptBP (0 % positive) by inducing oestrus in ovariectomised rats after injection of 100 mg of the test substance (Dodds and Lawson, 1938). Combined, the available information indicates a slightly higher oestrogenic activity of ptAP compared to ptBP but the data are too limited to extrapolate to the *in vivo* situation in higher tier animal studies. Nonetheless, based on read-across, ptAP might fulfil the criteria for ED for human health similar to ptBP.

T-modality

With respect to the T-modality, similar to ptBP, ptAP did not show interaction with TR (Kitagawa et al., 2003; Paul-Friedman et al., 2019), and was ambiguous as an inhibitor for TPO with less than 50 % efficacy (Paul Friedman et al. (2016); see also the Comptox dashboard[10]). Other published *in vitro* data for ptAP are not available for the T-modality. A 90-day oral gavage guideline study (according to US EPA OPPTS 870.3100) did not report on abnormal findings for thyroid weight, histopathology and hormone levels (MPI Research

[9] https://comptox.epa.gov/dashboard/chemical/bioactivity-toxcast-models/DTXSID8021771
[10] https://comptox.epa.gov/dashboard-viztool//plot?representative_sample=false&url_env=https://comptox.epa.gov/dashboard-api/&assay_endpoint_nm=CCTE_Simmons_AUR_TPO_dn&dsstox_id=DTXSID8021771

Inc, 2012) (see also 7.9.5.3. and 7.10.2.1). However, as it is not part of guideline testing, the study did not utilise non-albino rats and did not explore the occurrence of thyroid autoantibodies that could have further informed on putative autoimmune thyroid effects. Therefore, ptAP, similar to ptBP, is considered inconclusive with respect to the T-modality.

In conclusion, in view of the developments described under Sections 4.1 and 7.2, the eMSCA is of the opinion that it is not justified to uphold the requirement for additional animal testing.

7.10.3. Conclusion on endocrine disrupting properties and related classification and labelling (combined)

ptBP and ptAP cause adverse and population-relevant effects in several fish species plausibly linked to endocrine (in particular oestrogenic) activity. Consequently, both substances were identified as SVHC due to their ED properties for the environment. Based on the new CLP hazard classes and their criteria, the eMSCA considers that ptBP and ptAP are likely to fulfil the criteria for harmonised classification as ED Cat.1 for the environment.

With regard to human health, a two-generation reproductive toxicity study with ptBP demonstrates effects on several EAS-mediated/sensitive parameters related to fertility and sexual function. Mechanistic *in vitro* and *in vivo* studies for both, ptBP and ptAP, show interaction with ER (oestrogenic/anti-oestrogenic), and there is additionally some evidence for interference with steroidogenesis. The adverse effects on EAS-mediated/sensitive parameters seen in the two-generation study are possibly linked to the endocrine activity of ptBP. Therefore, ptBP, and via read-across, ptAP might fulfil the definition of an ED for human health according to WHO and the newly adopted CLP criteria. This presumption is supported by the fact that ptBP and ptAP have been identified as ED for the environment due to adverse effects in fish plausibly linked to endocrine (oestrogenic) activity. Regarding the T-modality, there remains a concern for autoimmune thyroid effects since both substances are considered as inducers of vitiligo, a disorder that is strongly linked to AITD.

7.11. PBT and vPvB assessment

Not relevant for this substance evaluation.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

In order to identify possible risks, the eMSCA checked the CSRs on whether the exposure scenarios for workers were complete, plausible and well documented regarding relevant uses, exposure routes and targeted exposure collectives. The efficiency of the proposed risk management measures was evaluated in order to clarify whether further risk management options need to be considered. In the registration dossiers worker exposure assessments were provided based on modelled data.

The CSRs of ptBP and ptAP take into account the occupational life cycle, *inter alia* the use as a monomer in the production of resins and polymers and as an intermediate in the production of derivatives. ptBP and ptAP are obtained and used either as flakes or in a molten form at elevated temperatures covered by a nitrogen blanket. The handling of flakes, inhalation and dermal exposure of workers were assessed by the tier 1 models ECETOC TRA v3 and extended TRA. Measured data were not submitted. Some measurement data related to the use of ptBP flakes was available from the RAR (EU, 2008). Since the use pattern and dustiness of ptBP and ptAP are very similar these measurement data can be considered as analogous for ptAP (Kosaka et al. (1989); Ebner et al. (1979)).

Inhalation exposure to ptBP and thus to ptAP dust during loading of reactors exceed the DNEL by a factor of 2.

For using the molten substances, e.g. unloading bulk containers and bulk quantity additions, exposure was not assessed. At the workplaces, the substances occur in a molten form at elevated temperatures leading to inhalation exposure and as solidified melt on equipment surfaces (gaskets, flanges etc.) after cooling down causing dermal exposure.

Based on calculations using a tier 1 model it was assumed that this situation leads to considerable higher inhalation exposure levels than using flakes. However, the possible exposure reducing effect of the nitrogen blanket cannot be considered in tier 1 models. It was not possible to calculate inhalation and dermal exposure levels using a tier 2 model due to a lack of information on the details of the exposure relevant parameter. Following fulfilling the request of the first substance evaluation decision, the identified risks that arose from exposure assessment of dermal and inhalation exposure of ptBP and ptAP were clarified by a higher tier assessment (ART 1.5) provided by the registrants and no further concerns remain.

According to the lead registrants ptBP and ptAP are used in a variety of industrial settings. The substances are monomers or intermediates in the production of polymers, which in turn are further processed into a range of products, e.g. paints, colourants, adhesives. ptAP is also used for perfumes and fragrances. The corresponding scenarios were part of the first exposure assessment.

With an update of the lead dossiers for ptBP and ptAP some industrial and all professional end uses and all consumer uses were removed. The removal of uses was specifically related to scenarios where the substance occurs as a residual monomer (e.g. paints, lacquers and varnishes, construction materials, process regulators, adhesives, binding agents, fillers). However, for ptBP two co-registrants remain which support professional and consumer uses in their current dossiers. The corresponding dossiers have not been updated for more than 10 years, i.e. even since before the start of the substance evaluation process.

Besides this, ptBP is used as a hardener in end products in higher concentration up to 30 %, e.g. coatings and paints, fillers, putties, thinners, polymer preparations and compounds, as a component of two part-coatings. In the corresponding scenarios, a component containing up to 30 % ptBP is mixed with other materials and thus diluted to an application concentration of up to 6 %. The identified risk with regard to dermal exposure for the application of liquid and solid end products containing ptBP was clarified by a higher tier assessment by the registrants for ptBP and no further concerns remain.

The eMSCA considers that the industrial uses such as for the manufacture polymers and coating products, building and construction work (described on the dissemination site of ECHA for ptBP) in many cases also indicate applications in the professional field. This could be taken into account and further information gathered in follow-up regulatory substance processes.

7.12.1.2. Consumer

7.12.1.2.1. ptBP

Although the majority of registrants including the lead registrant removed all consumer uses, ptBP is listed for the use in paints, thinners, paint removers and adhesives and sealants on ECHA’s dissemination site. It should however be noted that the corresponding registrations have not been updated since 2013. The eMSCA cannot conclude whether these uses correspond to real supply chains in 2023.

Consumer uses of ptBP and its derivatives, and ptBP residues in polymers like polycarbonates and phenolic resins have also been described in the EU-RAR (EU, 2008).

In the SPIN database, with latest product data from 2020, one or several products in Sweden, Denmark and Norway still indicate a probable or very probable consumer exposure. Consumer products have been explicitly registered in Sweden and Norway. Also, a very probable use in article productions is indicated.

In surveys of the German online market by the eMSCA, substitution of ptBP in several products was observed, and the general impression is that direct consumer uses of ptBP are being substituted. However, the substance was still occasionally found in March 2023, e.g. in two hardeners for epoxy fillers, in an adhesive for pond liners and in a spar varnish. In an Assessment of Regulatory Needs (ARN) (ECHA, 2021) by ECHA, consumer uses of substances containing ptBP as a component or impurity have been compiled based on registration data. These consumer uses cover the following product categories: adhesives, coatings, paints, inks, fuel and fuel additives, lubricants and greases, washing and cleaning products.

In addition, there is a low but continuous exposure of the general population to ptBP from articles, including food contact materials, and via the environment.

Overall, the eMSCA concludes that there is the need of a better understanding of residual concentrations of ptBP in consumer articles and mixtures. Due to the multiple potential sources of ptBP residues, a quantitative exposure assessment is complex and out of scope of the present substance evaluation. Therefore, the concern is unresolved.

7.12.1.2.2. ptAP

According to ECHA's dissemination site, consumer uses were not registered for ptAP. In the SPIN database, with latest product data from 2020, one or several products indicate a probable consumer exposure, and consumer preparations are still explicitly registered in Sweden. In addition, a very probable use in article productions is indicated in the SPIN database[11]. In an internet survey of the German online market in March 2023, consumer products containing ptAP could not be identified.

Overall, the eMSCA concludes that direct consumer uses of ptAP have almost disappeared. Therefore, the concern is considered clarified.

7.12.2. Environment

Based on the uses of ptBP and ptAP, there are two general emission pathways to the environment: Firstly, environmental exposure to ptBP or ptAP respectively might arise via direct emissions from industrial sites, where the substance itself is used. Secondly, ptBP or ptAP monomers respectively might be indirectly released from polymers, either by migration of residual free monomers or by degradation of the polymer. Releases from polymers can occur during all life cycle stages. While industrial emissions are restricted to only few locations, releases from polymers are expected to occur wide dispersive. Furthermore, ptBP can be formed via environmental degradation of precursor substances (see e.g. (Trebse et al., 2016)).

There are only few measured values available for ptBP. The data had been summarised in section 3.1.4.2 of the EU RAR.

During substance evaluation a literature search has been conducted for additional values measured in Europe and published since 2003 (the date of the last literature search for the EU RAR was 2004). The following additional values were found:

[11] A search of the online SPIN database (http://www.spin2000.net/spinmyphp/) was conducted in March 2023.

Table 17

Measured values for freshwater		
Site	**ptBP in water [ng/L]**	**Reference**
10 sampling sites along the river Elbe and at the mouth of 5 of its tributaries, all in Germany	Detected at 6 sites and at the mouth of the tributaries Mulde and Schwinge Elbe: 2.0 to 66.0 Mulde: 4.8 Schwinge: 2.4	(Stachel et al., 2003)
River water, 2 samples	Not detected	(Garcia-Jares et al., 2014)
France: 291 raw water samples (surface water and ground water) and 291 tap water samples from all French departments, 29 French brands of bottled water, 5 French drinking water networks with epoxy resin coated pipes	**Raw water** detected in one surface water sample: 340 **Tap water** Not detected **Bottled water** Detected in all water bottled in recently manufactured polycarbonate containers (3 brands, 4 to 5 containers each): 247 +/-10, 44 +/-5, 162 +/-45 Not detected in water bottled in older containers **Water network with resin coated pipes** Not detected	(Colin et al., 2014)

Table 18

Measured values for freshwater sediment		
Site	**ptBP in sediment [µg/kg dw]**	**Reference**
10 sampling sites along the river Elbe and at the mouth of 2 of its tributaries, all in Germany	Detected at 4 sites and at the mouth of the tributary Saale Elbe: 2.6 to 185 Saale: 3.1	(Stachel et al., 2003)

Table 19

Measured values for marine water		
Site	**ptBP in water [ng/L]**	**Reference**
North Sea, 4 sites in vicinity of Ekofisk oil production platform and reference site	Detected in 3 of 4 samples in vicinity of oil production platform: 0.017 to 0.045, reference site: 0.047	(Harman et al., 2009)
North Sea, 4 sites at Statfjord oil field and reference site	Detected in two samples	(Harman et al., 2010)

Table 20

Measured values for produced water from offshore oil installations		
Site	**ptBP in produced water [ng/L]**	**Reference**
9 oil installations in the North Sea and Norwegian Sea	164 to 653	(Boitsov et al., 2007)

Table 21

Measured values for wastewater treatment plants		
Site	**ptBP in water [ng/l]**	**Reference**
3 samples of effluent water and 2 samples of influent water	Detected in one effluent water sample: 113	(Garcia-Jares et al., 2014)
Effluent and influent STP water samples, Area of Tarragona, Catalonia, Spain	Influent water sample: 460 Effluent water sample: 300	(Brossa et al., 2004)

Overall, the more recent values are in the same order of magnitude as the values documented in the EU RAR. ptBP was found in different environmental compartments although it is often only detected in part of the samples. However, the data available is based on few selected sampling sites and no regular and widespread monitoring values do exist. Therefore, it is not possible to conclude on general environmental levels of ptBP within Europe or on the temporal development of environmental concentrations.

ptBP is contained in produced water, which is released into the marine environment by offshore oil exploration activities. Produced water originates from the oil reservoirs. It is brought up together with the oil, is then separated and released. Produced water contains a vast number of organic compounds, including alkylphenols. In produced water from 9 Norwegian oil installations 164 to 653 ng/L ptBP were detected, alongside with 51 other known alkylphenols and a large number of unknown alkylphenols (Boitsov et al., 2007). After release into the marine environment produced water is quickly diluted. In marine water 0.017 to 0.047 ng/L ptBP were detected in one single study (Harman et al., 2009).

Further uses assessed:

Another known application is the production and use of Oilfield chemicals.

The EU RAR considered the production of ptBP derivatives used as specialist surfactants to separate crude oil in aqueous refinery effluent from offshore oilfields. The derivatives are

manufactured by ethoxylation of ptBP/formaldehyde resins. The EU RAR concluded environmental release of ptBP from this application is restricted to phenolic resin production. Accordingly, this use is not considered relevant for the CSR. There are measurements of alkylphenol concentrations in produced water of 9 oil installations in the North Sea and Norwegian Sea (Boitsov et al., 2007). Produced water is the water which is brought up together with the oil from the oil reservoirs and is then separated from the oil. It also contains chemicals used for oil extraction. Between 164 and 653 ng/L ptBP were measured in produced water. However, after release to the environment this water is quickly diluted. In marine water only 0.017 to 0.047 ng/L ptBP were detected (Harman et al., 2009). However, altogether 354 alkylphenols have been detected in produced water, of which 52 could be identified (Boitsov et al., 2007). Endocrine effects have been observed following exposure to produced water (Harman et al., 2010). The contribution of ptBP is minor compared to the total amount of alkylphenols released with produced water. It is not possible to assign any effects to one specific component released with produced water. Effects will be rather caused by the combination of all endocrine active substances emitted due to summation of effects. Therefore, this concern cannot be clarified within the scope of this substance evaluation on ptBP.

For ptAP only very few measured values are available. Only one publication with measured environmental values for ptAP could be found. All data available is based on few selected sampling sites and ptAP was not part of any regular and widespread monitoring programme. Therefore, it is not possible to conclude on general environmental levels of ptAP within Europe or on the temporal development of environmental concentrations.

Table 22

Measured values for freshwater		
Site	**ptAP in water [ng/l]**	**Reference**
10 sampling sites along the river Elbe and at the mouth of 5 of its tributaries, all in Germany	Detected at 6 sites and at the mouth of the tributaries Mulde and Schwinge Elbe: 1.7 to 4.9 Mulde: 4.8 Schwinge: 5.9	(Stachel et al., 2003)

7.12.3. Combined exposure assessment

In a meeting in July 2014 the registrants stated that two or more industrial processes do not occur at the same site. Therefore, an aggregated exposure on a local scale by industrial processes should not occur.

As described above, at the beginning of the evaluation process the registration contained the description of several consumer uses of products containing ptBP or ptAP, respectively.

In the follow-up the lead dossiers for ptBP and ptAP were updated and some industrial, all professional and all consumer uses were removed. Two registrants of ptBP remain which support professional and consumer uses in their current dossiers. However, the corresponding dossiers have not been updated for more than 10 years, i.e. even since before the start of the substance evaluation process. Therefore, the role of these wide dispersive uses is somehow unclear.

For ptAP an assessment of the aggregated exposure due to all wide dispersive uses has not been performed by the registrants in the updated dossiers, as wide dispersive uses were removed from the CSR. In the earlier version of the dossiers the combined exposure

due to all widespread uses had been assessed. For ptBP the combined exposure due to all wide dispersive uses was briefly assessed in the registration.

The eMSCA suspects that, for some uses, the environmental exposure might be underestimated. Furthermore, the tonnage considered by each registrant makes up only about a fraction of the total EU tonnage. For aggregated exposure assessment the total EU tonnage should be used. The level of environmental exposure could not be assessed readily based on the available data. The data gaps are mainly concerning the uses of polymers.

An assessment of human health risks for the general population due to aggregated exposure from multiple sources was out of the scope of the present substance evaluation.

7.13. Risk characterisation

7.13.1. Worker

Considering the physicochemical properties of ptBP or ptAP respectively and their industrial uses, workplace exposure occurs mainly via inhalation and dermal contact. For quantitative risk characterisation, modelled inhalation and dermal exposure data is compared to the long-term systemic DNEL (inhalation) of 0.5 mg/m^3 and to the long-term systemic DNEL (dermal) of 0.07 mg/kg bw/d, respectively. The risk characterization ratios (RCR) per each route of exposure are then added to calculate the combined RCR for each exposure scenario. Both DNEL values are based on data derived from collectives exposed occupationally to ptBP where vitiligo-like skin depigmentation was identified as the earliest and most sensitive adverse systemic effect (see Section 7.9.6 for details).

As described in the CSRs ptBP and ptAP are manufactured as a solid (flakes) as well as in a molten form. Both forms are used as a starting material for further processing. Due to the lack of measurement data the exposure assessment for inhalation and dermal exposure was performed by the eMSCA on estimations with the actual version of ECETOC TRA (v3).) and analogous data. The initially identified risks could be clarified by higher tier assessments (see Section 7.12.1.1). This also applies to end products with ptBP as hardener.

7.13.2. Consumer

Risk characterisation for consumers was not performed as the existing data on consumer exposure did not allow a reliable quantification.

7.13.3. Environment

ptBP and ptAP are ED for the environment based on the assessment of the eMSCA. Since the start of the substance evaluation process, both substances have been identified as SVHC based on these properties. Therefore, exposure of the environment should be minimised. The lowest LOECs for endocrine effects are in the range of only a few µg/L. Therefore, environmental concentrations of some 100 ng/L, which is far below the PNEC, might be relevant for endocrine effects. The PEC values for several uses are in such a range that might already cause endocrine effects.

Additionally, some shortcomings in the exposure assessment indicate that environmental risks might be underestimated. Based on the communication with the registrants it has to be assumed that the registrants have no further information on these points. Therefore, the eMSCA considers that it cannot be excluded that risks are not adequately controlled. While further exposure data would need to be collected to improve the environmental exposure assessment of ptBP and ptAP, the eMSCA proposes to consider a potential restriction proposal. Such information may be obtained through this other regulatory process. Therefore, the eMSCA concludes that no further information is requested under this substance evaluation.

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7.15. Abbreviations

AF	assessment factor
AGS	German Committee on Hazardous Substances
AGW	Arbeitsplatzgrenzwert
AITD	autoimmune thyroid disease
AR	androgen receptor
ARN	Assessment of Regulatory Need
BAT	Biological Tolerance Value at the Workplace (Biologischer Arbeitplatztoleranzwert)
BOEL	binding occupational exposure level
bw	body weight
CLP	classification labelling packaging
CoRAP	continuous rolling action plan
CSR	chemical safety report
DNEL	derived no effect level
EAS	oestrogen/androgen/steroidogenesis (-modality)
ECHA	European Chemicals Agency
ED	endocrine disruptor(s)/disruptive/disrupting
ELoC	equivalent level of concern
eMSCA	evaluating Member State Competent Authority
Env	environment
ES	exposure scenario
EU	European Union
EPA	Environmental Protection Agency
ER	oestrogen receptor
GNPD	global new products database
LD50	lethal dose 50
LOAEL	lowest observed adverse effect level
MAK	maximum workplace concentration (Maximale

	Arbeitsplatzkonzentration)
MoA	mode of action
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OC	operational condition
OEL	occupational exposure level
OECD	organization for economic co-operation and development
ptAP	*p*-(1,1-dimethylpropyl)phenol, *p-tert*-amylphenol
ptBP	*p-tert*-butylphenol
PC	product category
POD	point of departure
ppm	parts per million
PROC	process category
RAC	Risk Assessment Committee
RAR	risk assessment report
RDT	repeated-dose toxicity
RMM	risk management measure
RMOA	risk management option analysis
RoI	registry of intention
ROS	reactive oxygen specie
SCCS	Scientific Committee on Consumer Safety
SDS	safety data sheet
SEv	substance evaluation
SVHC	Substance(s) of very high concern
STOT-SE	Specific Target Organ Toxicity – Single Exposure
STOT-RE	Specific Target Organ Toxicity – Repeated Exposure
STP	sewage treatment plant
T	thyroid(-modality)
T3	triiodothyronine
T4	thyroxine (tetraiodothyronine)
Tg	thyroglobulin
TG	test guideline
tpa	tonnage per year
TPO	thyroid peroxidase
TR	thyroid hormone-receptor
TRGS	technische Regeln für Gefahrstoffe
TSH	thyroid-stimulating hormone
TSHR	TSH receptor
TWA	time weighted average
UV	ultraviolet
VTG	vitellogenin
WHO	World Health Organisation
XBP1	X-box binding protein 1