Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

4-tert-butylphenol and 4-tert-pentylphenol

Evaluation statement

30 June 2022

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AICIS evaluation statement

Subject of the evaluation

4-tert-butylphenol and 4-tert-pentylphenol

Chemicals in this evaluation

Name	CAS registry number
Phenol, 4-(1,1-dimethylethyl)-	98-54-4
Phenol, 4-(1,1-dimethylpropyl)-	80-46-6

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to the environment.

Parameters of evaluation

This evaluation considers the environmental risks associated with the industrial uses of 4-tert-butylphenol (CAS RN 98-54-4) and 4-tert-pentylphenol (CAS RN 80-46-6). These chemicals have been assessed for their risks to the environment according to the following parameters:

- Default Australian introduction volume of 100 tonnes per annum for 4-tert-pentylphenol.
- Reported Australian introduction volume of 10–100 tonnes per annum for 4-tert-butylphenol.
- Industrial uses listed below in the 'Summary of Use' section.
- Expected emission into sewage treatment plants (STPs) due to consumer and commercial use.

These chemicals have been assessed as a group as they are structurally similar and are present in related industrial products.

Summary of evaluation

Summary of introduction, use and end use

The chemical, 4-tert-butylphenol, has reported Australian use in surface coatings. There is currently no specific information about the introduction, use and end use of 4-tert-pentylphenol in Australia.

Chemicals in this group are predominantly used as intermediates in the production of polymeric resins and other chemicals. The chemical 4-tert-butylphenol is used as an antioxidant in rubber, phenolic/epoxy resins and cellulose ester plastics. Polymers manufactured from the chemical are used in the following products according to reported international use data:

- Adhesive and sealant products
- Ink, toner and colourant products
- Paint and coating products
- Plastic and polymer products.

The chemical 4-tert-pentylphenol is used as an antimicrobial in cleaning agents although industrial use of the chemical as an antimicrobial is not expected to be widespread.

Reported volumes from international jurisdictions indicate that 4-tert-butylphenol is used in the EU at up to 100 000 tonnes per year, and in the USA at 22 680 tonnes (50 000 000 lb) per year. Reported volumes of 4-tert-pentylphenol indicate that the chemical is used in the EU at up to 1000 tonnes per year and in the USA at 9072 tonnes (20 000 000 lb) annually.

Environment

Summary of environmental hazard characteristics

According to Australian environmental hazard thresholds and based on the available data these chemicals are:

- Not Persistent (Not P)
- Not Bioaccumulative (Not B)
- Toxic (T).

Environmental hazard classification

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for environmental hazards as follows (UNECE 2017). This does not consider classification of physical hazards and health hazards.

For 4-tert-butylphenol:

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short term)	Aquatic Acute 2	H401: Toxic to aquatic life
Hazardous to the aquatic environment (long term)	Aquatic Chronic 1	H410: Very toxic to aquatic life with long lasting effects

For 4-tert-pentylphenol:

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short term)	Aquatic Acute 2	H401: Toxic to aquatic life

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (long term)	Aquatic Chronic 2	H411: Toxic to aquatic life with long lasting effects

Summary of environmental risk

Chemicals in this group are closely related branched alkylphenols with similar industrial uses as intermediates. Other industrial uses of these chemicals include 4-tert-butylphenol used as an antioxidant and 4-tert-pentylphenol as an antibacterial ingredient. These chemicals are expected to be released to the aquatic compartment in treated sewage treatment plant (STP) effluent from their industrial uses.

Chemicals in this group are not persistent and not bioaccumulative, according to Australian categorisation criteria. However, these chemicals are toxic according to Australian categorisation criteria.

The predicted concentrations of chemicals in this group in Australian surface waters are below the level of concern (RQ <1) based on conventional ecotoxicity test endpoints. The industrial use of 4-tert-butylphenol and 4-tert-pentylphenol are; therefore, unlikely to pose a significant risk to the environment based on this metric. However, the RQ values may underestimate the environmental risks posed by these chemicals.

International jurisdictions have concluded that these chemicals have endocrine disrupting properties. The United Nations Environment Programme (UNEP) consider endocrine disrupting chemicals an emerging issue and have identified 4-tert-pentylphenol to be an endocrine disrupting chemical. The European Chemicals Agency (ECHA) have published recent reports on the two chemicals in this Evaluation Statement, concluding that they both have endocrine disrupting properties that give rise to an equivalent level of concern to those of PBT substances.

There are insufficient data to quantify the risks to the Australian environment from the endocrine related effects of these chemicals. However, according to the data presented in this evaluation, both 4-tert-butylphenol and 4-tert-pentylphenol have endocrine disrupting properties. They are endocrine active, and are able to cause adverse effects as a result of this endocrine activity to individual organisms. These effects are shown to occur at environmentally relevant concentrations. Considering the identified environmental hazards of these chemicals, environmental risks would be reduced if less hazardous alternatives are used by industry.

Conclusions

The conclusions of this evaluation are based on the information described in this Evaluation Statement.

The Executive Director is satisfied that the identified environmental risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

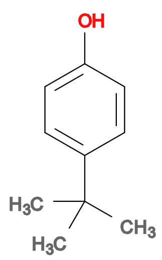
Supporting information

Rationale

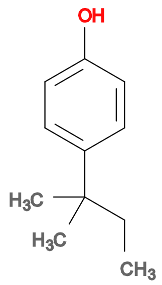
This evaluation considers the environmental risks associated with the industrial uses of 4-tert-butylphenol and 4-tert-pentylphenol, two closely related alkyl-substituted phenols. The evaluation of these chemicals has been conducted as a group due to their structural similarity and similar industrial uses.

The Evaluation Selection Analysis (ESA) of 4-tert-butylphenol and 4-tert-pentylphenol highlighted their potential to cause endocrine-mediated effects, which are of concern for the environment. This evaluation includes further refinement of the risk characterisation of chemicals in this group and a more in depth assessment of the available environmental hazard and exposure information for these chemicals.

Chemical identity

CAS RN	98-54-4
Chemical name	Phenol, 4-(1,1-dimethylethyl)-
Synonyms	Phenol, p-tert-butyl- p-tert-Butylphenol 4-tert-butylphenol 4TBP
Structural formula	
Molecular formula	$C_{10}H_{14}O$
Molecular weight (g/mol)	150.22
SMILES	CC(C)(C)C1=CC=C(C=C1)O
Chemical description	-

CAS RN	80-46-6

Chemical name	Phenol, 4-(1,1-dimethylpropyl)-
Synonyms	4-tert-pentylphenol 4-tert-amylphenol para- (or p-) tert-amylphenol para- (or p-) tert-pentylphenol 4TPP pentaphen
Structural formula	
Molecular formula	$C_{11}H_{16}O$
Molecular weight (g/mol)	164.25
SMILES	CCC(C)(C)C1=CC=C(C=C1)O
Chemical description	-

Relevant physical and chemical properties

Measured physical and chemical property data for 4-tert-butylphenol and 4-tert-pentylphenol were retrieved from the databases included in the OECD QSAR Toolbox (OECD 2020), dossiers submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the European Union (EU) (REACHa ; REACHb), and the OECD Screening Information Dataset (SID) initial assessment report (OECD 2000).

The Henry's Law Constant values were calculated from measured values for water solubility and vapour pressure (US EPA 2017).

Chemical	4-tert-butylphenol	4-tert-pentylphenol
Physical form	Solid	Solid
Melting point	99.2°C (exp.)	94.7°C (exp.)
Boiling point	238°C (exp.)	255°C (exp.)
Vapour pressure	0.5 Pa at 20°C (exp.)	< 5 Pa at 20°C (exp.)

Water solubility	607.2 mg/L at 25°C (exp.)	193 mg/L at 21°C (exp.)
Henry's law constant	0.125 Pa·m^3/mol (calc.)	0.206 Pa·m^3/mol (calc.)
Ionisable in the environment?	No	No
pKa	10.16 at 25°C (exp.)	10.4 (calc.)
log K_{ow}	3.3 at 25°C (exp.)	3.9 at 25°C (calc.)

Chemicals in this group are weak acids. The phenolic functional groups are unlikely to dissociate under normal environmental conditions.

Introduction and use

Australia

No current specific Australian use, import, or manufacturing information has been identified for 4-tert-pentylphenol.

The chemical 4-tert-butylphenol has a reported use in Australia in surface coatings. The total volume of the chemical introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was in the range of 10–100 tonnes (NICNAS 2016).

International

Chemicals in this group, 4-tert-butylphenol and 4-tert-pentylphenol, are present on the United States (US) EPA High Production Volume (HPV) list (US EPA 2020), with annual use volumes of 22 680 and 9072 tonnes respectively (US EPA 2016). In the European Economic Area (EEA), 4-tert-butylphenol and 4-tert-pentylphenol are registered for use in the range of 10 000–100 000 and 100–1000 tonnes per year respectively (REACHa; REACHb).

Chemicals in this group are reportedly manufactured and/or imported at 10 000 to 20 000 tonnes per annum in Japan from 2013 – 2019 (NITE 2020). In the Nordic countries, the average annual use volume of 4-tert-butylphenol over a five year period from 2015–2019 was 181 tonnes (SPIN).

The main use of 4-tert-butylphenol by volume is as an intermediate in the production of polycarbonate, phenolic and epoxy resin polymers (EU RAR 2008). The polymers based on 4-tert-butylphenol have commercial uses as adhesives and in paints and coatings (REACHa).

Reportedly, 4-tert-butylphenol is used as an antioxidant in rubber, phenolic/epoxy resins and cellulose ester plastics (FPF 2019; US EPA 2014b). It is authorised for use in food packaging contact materials under Annex I of Regulation (EU) No 10/2011 (EC 2011).

Available information indicates 4-tert-pentylphenol is used as an intermediate for the synthesis of fragrances, phenolic resins and vulcanising agents for the curing of rubber (AICIS 2021; REACHb). The polymers based on 4-tert-pentylphenol have commercial uses in paints and coatings and printing inks (Environment Agency 2008). It is also used as an antibacterial ingredient in cleaning and washing agents (US EPA 2014a). There is no evidence from available databases that this chemical is used in consumer industrial products, indicating that it is not likely to be widely available for domestic use. Uses identified in the Consumer Product Information Database were limited to disinfectants which have non-industrial uses in Australia (DeLima Associates).

The use of 4-tert-butylphenol in cosmetics is restricted in multiple jurisdictions. The chemical is listed as a prohibited ingredient in fragrances and cosmetics by the:

- International Fragrance Association (IFRA) 50th amendment (IFRA 2021)
- EU Cosmetics Regulation 1223/2009 Annex II (EC)
- ASEAN Cosmetic Directive Annex II (HSA 2020)
- New Zealand Cosmetic Product Group Standard (NZ EPA 2020)
- Health Canada List of Prohibited and Restricted Cosmetic Ingredients (Government of Canada 2019).

Existing Australian regulatory controls

Environment

The use of 4-tert-butylphenol and 4-tert-pentylphenol is not subject to any specific national environmental regulations.

International regulatory status

United Nations

Chemicals in this group are not currently identified as a Persistent Organic Pollutant (UNEP 2001), an ozone depleting substance (UNEP 1987), or hazardous substance for the purpose of international trade (UNEP & FAO 1998).

The chemical 4-tert-pentylphenol is identified as an endocrine disrupting chemical in an International Panel on Chemical Pollution (IPCP) report commissioned by United Nations Environment Programme (UNEP) (UNEP 2018), based on the completed 4-tert-pentylphenol EU REACH SVHC assessment (ECHA 2016b).

European Union

Both chemicals in this group are listed on the candidate list of substances of very high concern (SVHC) due to ‘endocrine disrupting properties which cause probable serious effects to the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances’ (ECHA 2020).

Environmental exposure

Chemicals in this group are primarily used as intermediates in the manufacture of polycarbonate and phenolic/epoxy resin polymers (REACHa ; REACHb). These uses are not expected to result in high emissions to the environment as they result in these chemicals irreversibly bound within a polymer matrix. The quantities of residual unreacted 4-tert-butylphenol in polycarbonate products were reported to be <5 parts per million (ppm) (EU RAR 2008).

The chemical, 4-tert-butylphenol, is also used as an antioxidant in food packaging, rubber and phenolic/epoxy resins (US EPA 2014b). As 4-tert-butylphenol is not irreversibly bound within the polymer matrix, release into the environment may occur from 4-tert-butylphenol migration to the surface of these articles and subsequent release due to abrasion and wear from normal use. The chemical may also be released to the environment through degradation processes of non-polymer materials.

The chemical, 4-tert-pentylphenol, is present as an antibacterial ingredient in washing agents, although this use may be limited to non-industrial uses (Environment Agency 2008; US EPA 2014a).

Depending on degradation and partitioning processes of chemicals in sewage treatment plants (STPs), some fraction of the quantity of chemicals in wastewater entering STPs can be emitted to the air compartment, to rivers or oceans in treated effluent, or to soil by application of biosolids to agricultural land (Struijs 1996). The emissions of 4-tert-pentylphenol and 4-tert-butylphenol to environmental surface waters, sediment, soil and air are considered as part of this evaluation.

Environmental fate

Partitioning

Chemicals in this group are expected to partition to the soil and water compartment after release to the environment from their industrial use.

Chemicals in this group are neutral organic chemicals that are moderately soluble in water. The calculated Henry's Law Constants for 4-tert-butylphenol and 4-tert-pentylphenol (0.125 and 0.206 $Pa \cdot m^3/mol$), indicate that these chemicals are moderately volatile from water and moist soil. The calculated soil adsorption coefficient for 4-tert-butylphenol (log K_{OC} = 3.1) and 4-tert-pentylphenol (log K_{OC} = 3.4) indicates these chemicals have a low mobility in soil (US EPA 2017).

Calculations with a standard multimedia partitioning (fugacity) model assuming equal and continuous distributions to air, water and soil compartments (Level III approach) predict that 4-tert-butylphenol and 4-tert-pentylphenol will mainly partition to the soil compartment (81% and 80% respectively) (US EPA 2017).

Degradation

Chemicals in this group are not persistent. They will biodegrade under aquatic aerobic conditions and rapidly degrade in the atmosphere.

Hydrolysis is unlikely to be a major dissipation pathway in the environment for 4-tert-butylphenol and 4-tert-pentylphenol. Chemicals in this group are not expected to degrade by hydrolysis under aqueous conditions based on the lack of hydrolysable functional groups. In accordance with the OECD Test Guideline (TG) 111, 4-tert-butylphenol was found to be stable in the water compartment at pH levels 4, 7 and 9 (OECD 2000).

The chemical, 4-tert-butylphenol, is biodegradable based on a study conducted in accordance with OECD TG 301B (REACHa). The measured degradation across two concentrations was 58.5% (5 mg/L) and 63.5% (10 mg/L) theoretical carbon dioxide ($ThCO_2$) within 28 days. A second study conducted according to OECD TG 301F found that 42%

(at 25 mg/L) and 60% (at 15 mg/L) of 4-tert-butylphenol degraded within the 28 day duration of the test.

In a separate study following OECD TG 301A, 98% of 4-tert-butylphenol degraded over 28 days (REACHa). However, the inoculum used in this study was likely adapted to 4-tert-butylphenol as it was derived from a municipal STP in a heavily industrialised area. This study demonstrates that 4-tert-butylphenol can be fully mineralised, but it cannot be used to evaluate the ready biodegradability of the substance.

The chemical, 4-tert-pentylphenol, is readily biodegradable based on a screening test conducted in accordance with OECD TG 301B, with 73% biodegradation measured by dissolved organic carbon (DOC) removal over 28 days (REACHb).

Both 4-tert-butylphenol and 4-tert-pentylphenol are expected to rapidly degrade in the atmosphere following reaction with hydroxyl radicals, with a calculated half-life of of 3.2 and 3.1 hours respectively (US EPA 2017).

Bioaccumulation

Chemicals in this group have low potential to bioaccumulate in aquatic life.

The measured octanol-water partition coefficients of 4-tert-butylphenol and 4-tert-pentylphenol (log K_{OW} of 3.3 and 3.9 respectively) are below the Australian categorisation threshold for bioaccumulation hazards in aquatic organisms (log $K_{OW} \geq 4.2$), indicating low potential for bioaccumulation (EPHC 2009).

Measured data indicates that 4-tert-butylphenol has low potential to bioconcentrate in fish. A study conducted in accordance with OECD TG 305C reported a lipid-normalised bioconcentration factor (BCF) value of 20-48 litres per kilogram (L/kg) wet weight (wwt) in *Cyprinus carpio* (carp) (REACHa). A separate study with no test guideline stated, reported a BCF value of 120 L/kg in *Leuciscus idus melanotus* (orfe) (REACHa). These values are below the Australian categorisation threshold for bioconcentration in aquatic organisms (BCF ≥ 2000) (EPHC 2009).

Environmental transport

Chemicals in this group are not expected to undergo long range transport based on their expected short half-lives in the environment.

Predicted environmental concentration (PEC)

The predicted environmental concentrations of 4-tert-butylphenol and 4-tert-pentylphenol in Australian surface waters are 100 ng/L and 10 ng/L respectively, based on Australian and international monitoring data.

In an Australian monitoring study, 4-tert-butylphenol was detected at below the limits of quantification in samples from three different sources; secondary treated wastewater effluent (<100 nanogram per litre (ng/L)), drinking water (<5 ng/L), and surface water sampled from a small creek in an urban area of the Gold Coast (<20 ng/L). (Leusch et al. 2018). Differences in limits of quantification in this study were due to differing levels of analyte enrichment between samples. This study reported similar results for equivalent samples from Germany, France, South Africa, and Spain. In the Netherlands, higher concentrations of 300 ng/L and 490 ng/L were found in treated wastewater samples and surface water samples respectively.

In international studies, 4-tert-butylphenol has been detected in STP influent and effluent samples. Influent concentrations have been measured in the range of 0.021–3.2 µg/L (Barber et al. 2007; Rudel et al. 1998; Xu et al. 2016). Effluent concentrations vary depending on the level of treatment, with a concentration of 0.0696 µg/L measured following primary treatment (Xu et al. 2016) and concentrations of 0.016–0.035 µg/L measured after secondary treatment (Barber et al. 2006; Rudel et al. 1998). Monitoring studies conducted in Sweden and Austria reported influent concentrations in the range of 46–110 ng/L, and effluent concentrations in the range of 52–154 ng/L (EU RAR 2008).

The chemical, 4-tert-pentylphenol, has been detected in international STP influents. Influent concentrations in the range of 29–190 ng/L have been reported, with concentrations falling to below the detection limit of 4.5 ng/L in effluent samples after secondary treatment (Rudel et al. 1998).

These chemicals have been quantified in international surface water studies at concentrations in the range of 0.1–130 ng/L and 0.1–7.7 ng/L for 4-tert-butylphenol and 4-tert-pentylphenol respectively (Brossa et al. 2005; Heemken et al. 2001; Stachel et al. 2003). Some studies have found significantly higher concentrations; in surface water samples from the Yangtze river, 4-tert-butylphenol was detected in the range of 225–1121 ng/L (Liu et al. 2017) while in Singapore coastal waters 4-tert-butylphenol was found in the range of 10–2300 ng/L (Basheer et al. 2004). However, these sampling locations are unlikely to be representative of Australian surface waters.

A study of sediment samplings from Elbe River (Germany and Czech Republic) reported concentrations of 4-tert-butylphenol in the range of <1–185 micrograms per kilogram (µg/kg) and 4-tert-pentylphenol in the range of <1–77 µg/kg (Heemken et al. 2001; Stachel et al. 2003).

International aquatic biota samples have found concentrations of 4-tert-butylphenol. The chemical has been detected in aquatic organisms purchased from Singapore supermarkets, such as prawn (21.3 nanogram per gram (ng/g) wwt), crab (24 ng/g wwt), blood clam (8.8 ng/g wwt), white clam (6.5 ng/g wwt), squid (13.9 ng/g wwt) and Indian Scad (19 ng/g wwt) (Basheer et al. 2004).

In summary, the concentrations of 4-tert-butylphenol detected in Australian environmental surface waters are below 100 ng/L. Similar concentrations have been detected in samples from Germany, France, South Africa, and Spain. Higher concentrations have been detected in surface water samples from the Netherlands and very high concentrations have been detected in surface water samples from industrialised regions in Asia. However, these high concentrations from surface waters in heavily industrialised regions are not considered representative of Australian surface waters. The environmental concentration of 4-tert-butylphenol in Australian surface waters is unlikely to exceed 100 ng/L. To ensure a conservative risk estimate, the PEC in Australian surface waters is 100 ng/L. For 4-tert-pentylphenol, the surface water PEC is 10 ng/L.

Environmental effects

Effects on aquatic life

Acute toxicity

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms across three trophic levels were retrieved from the Registration Dossier for 4-tert-butylphenol and 4-tert-pentylphenol under EU REACH legislation (REACHa ; REACHb):

Taxon	Endpoint	Method
Fish	4-tert-butylphenol: 96h LC50 = 5.1 mg/L	*Oncorhynchus mykiss* (rainbow trout) OECD TG 203 Semi-static
	4-tert-pentylphenol: 96h LC50 = 2.5 mg/L	*Pimephales promelas* (fathead minnow) OECD TG 203 Flow-through
Invertebrate	4-tert-butylphenol: 48h EC50 = 4.8 mg/L	*Daphnia magna* (water flea) OECD TG 202 Immobilisation Static
	4-tert-pentylphenol: 48h EC50 = 2.7 mg/L	Water flea ISO 6341 Immobilisation Static
Algae	4-tert-butylphenol: 72h EC50 = 14 mg/L	*Raphidocelis subcapitata* (green algae) OECD TG 201 Growth rate Static
	4-tert-pentylphenol: 72h EC50 = 4.2 mg/L	*Pseudokirchneriella subcapitata* OECD TG 201 Growth rate Static

Chronic toxicity

The following measured no-observed-effect concentrations (NOEC) for model organisms across three trophic levels were retrieved from the Registration Dossier for 4-tert-butylphenol and 4-tert-pentylphenol under EU REACH legislation (REACHa ; REACHb):

Taxon	Endpoint	Method
Fish	4-tert-butylphenol: 128d NOEC = 0.01 mg/L	*Pimephales Promelas* (fathead minnow) OECD TG 210 Growth rate Flow-through
	4-tert-pentylphenol: 60d NOEC = 0.1 mg/L	*Oryzias latipes* (medaka) Extended OECD TG 210 Growth rate F1 generation Flow-through
Invertebrates	4-tert-butylphenol: 21d NOEC = 0.73 mg/L	*Daphnia magna* (water flea) OECD TG 202 Reproduction Semi-static
Algae	4-tert-butylphenol: 72h NOEC = 0.32 mg/L	*Raphidocelis subcapitata* (green algae) OECD TG 201 Growth rate Static
	4-tert-pentylphenol: 72h NOEC = 1.8 mg/L	*Pseudokirchneriella subcapitata* OECD TG 201 Growth rate Static

Marine acute toxicity

The following measured median lethal concentration (LC50) for model organisms across three trophic levels were retrieved from the Registration Dossier for 4-tert-pentylphenol under EU REACH legislation (REACHb):

Taxon	Endpoint	Method
Invertebrates	24h LC50 = 6.5 mg/L	*Artemia salina* (brine shrimp) British Standard Guideline (BSENISO 6341:1996)
	96h LC50 = 1.7 mg/L	*Crangon septemspinosa* (shrimp)

Effects on terrestrial life

Chemicals in this group are not expected to cause serious harm through oral exposure. Further information on the effects of 4-tert-butylphenol and 4-tert-pentylphenol on terrestrial organisms can be found in the Human Health IMAP Tier II assessment for 4-tert-butylphenol and Human Health AICIS Evaluation for 4-tert-pentylphenol (AICIS 2021; NICNAS 2016).

Endocrine effects

Chemicals in this group are endocrine active and appear to induce adverse effects in biota through an endocrine mediated mode of action. A detailed examination of this mode of action is beyond the scope of this assessment; however, summary findings from a selection of relevant peer reviewed scientific studies are presented below. A comprehensive examination of the available literature on this topic was recently published by ECHA in support of the listing of 4-tert-butylphenol and 4-tert-pentylphenol as SVHC for environmental concerns (ECHA 2016a; 2016b). Both reports concluded that these chemicals had endocrine disrupting properties, and the UNEP International Panel on Chemical Pollution has identified 4-tert-pentylphenol as an endocrine disrupting chemical (UNEP 2018).

Chemicals in this group act as oestrogen receptor agonists in in vitro tests (ECHA 2016a; 2016b). Competitive binding assays found that 4-tert-butylphenol and 4-tert-pentylphenol specifically bind to the oestrogen receptor of rainbow trout. This indicates the potential for 4-tert-butylphenol and 4-tert-pentylphenol to induce endocrine mediated effects at the organism level in fish. However, in vivo studies are required to determine whether the endocrine activity observed in in vitro studies will lead to adverse effects in environmentally relevant exposure scenarios. Therefore, this evaluation will focus on in vivo studies.

Indications of a chemical having an endocrine mediated mode of action can be determined by biomarkers and histological changes. Induction of an egg yolk precursor protein, vitellogenin (VTG), in female and male fish is a common biomarker to indicate an oestrogen agonist mode of action (OECD 2004). Histological changes in the OECD TG 229 for fish short term reproduction (OECD 2012) and the guidance document on the diagnosis of endocrine related histopathology in fish gonads (OECD 2010) describe the diagnostic endpoints for endocrine activity. The observed diagnostic gonad histopathological endpoints of 4-tert-butylphenol and 4-tert-pentylphenol include the presence of testis-ova, atrophy of germinal epithelium, increased oocyte atresia and gonadal duct feminisation. Additionally, reduced male secondary sex characteristics in fathead minnow or medaka and female skewed sex ratios are considered to be apical endpoints indicating an oestrogen agonist mode of action (OECD 2004).

Endocrine effects of 4-tert-butylphenol

A thorough review of the available literature on the endocrine effects of 4-tert-butylphenol was published in 2016 by the European Chemicals Agency (ECHA 2016a). A selection of these data are summarised below.

Two 4-tert-butylphenol exposure studies conducted on fish found effects characteristic of an endocrine mode of action, including VTG induction and histopathological effects. The first study, conducted according to OECD TG 234 (Fish sexual development test) on fathead minnow (*Pimephales promelas*), found a 128 day VTG induction LOEC of 255 µg/L in female fish. No VTG induction was observed in male fish. Gonadal duct feminisation of the testes was observed in male fish in the 255 µg/L exposure group. No significant changes to the sex ratio of the treated groups were observed, though an effect on the sex ratio was observed at 413 µg/L in a previous pilot study (ECHA 2013).

The second study was a non-standard study conducted with carp (*Cyprinus carpio*) with an exposure concentration range of 690–2300 µg/L over 28 days. VTG levels in male carp were elevated at all exposure concentrations compared to the control, but with an inverse dose-response relationship. Observed histopathological effects included a reduction of testicular size, necrosis of spermatozoa, reduced number of germ cells and atrophied germinal epithelium cells in male fish at all exposure concentrations.

A developmental study with pikeperch found significant effects on the sex ratio in pikeperch (*Sander lucioperca*) exposed to 4-tert-butylphenol. In this experiment, juvenile pikeperch were exposed to 4-tert-butylphenol for 28 days, starting from 60 days post hatch (dph). On the day immediately prior to 4-tert-butylphenol exposure, all fish were sexually undifferentiated. After 28 days (60 dph to 88 dph), fish in the water and solvent control groups were differentiated to 47–52% female and 53–48% male with no intersex fish observed. In the lowest concentration group of 1 µg/L 4-tert-butylphenol, the observed sex ratio was skewed towards female fish with 58.5% female, 31.5% male and 10% intersex. The sex ratio increased in a dose dependent manner with 68%, 80% and 98% female fish and 15%, 0%, and 0% male fish in the 10, 100 and 200 µg/L exposure groups respectively, with the remaining fish in each group classed as intersex. After an additional 56 days without exposure to 4-tert-butylphenol (88 dph to 144 dph), no significant changes to these sex ratios were observed for any treatment group. This study is strong evidence that 4-tert-butylphenol exerts effects through an endocrine mode of action, as effects upon sexual differentiation are an apical endpoint for an estrogen agonist mode of action (OECD 2004).

Endocrine effects of 4-tert-pentylphenol

A thorough review of the available literature on the endocrine effects of 4-tert-pentylphenol was published in 2016 by the European Chemicals Agency (ECHA 2016b). A selection of these data are summarised below.

Several in-vivo studies demonstrate that 4-tert-pentylphenol can induce VTG expression in fish, a biomarker of endocrine activity. The lowest VTG induction endpoint recorded is a 21 day LOEC of 10 µg/L in male fathead minnow, in a modified juvenile growth test. Other tests involving fathead minnow, zebrafish, and medaka also recorded VTG induction endpoints in the sub-milligram per litre concentration range, over exposure durations between 21 and 70 days.

The chemical can induce histological changes indicative of an endocrine mode of action (OECD 2010; 2012). In a 21 day exposure study, testes-ova were observed in male zebrafish and increased oocyte atresia observed in females at an exposure concentration of 787 µg/L. Increased spermatogonia and decreased spermatozoa were observed at 229 µg/L, indicating potential inhibition of spermatogenesis at this exposure concentration. In a 107 day extended early life stage test with fathead minnow, gonadal duct feminisation of the testes was observed in male fish at an exposure concentration of 56.6 µg/L, and testes-ova found at 188 µg/L.

Several studies have established the potential for 4-tert-pentylphenol to influence sexual differentiation in fish. In the same 107 day extended early life stage test from the previous paragraph, a skewed sex ratio in favour of female fish was observed starting from 188 µg/L 4-tert-pentylphenol. In the control group, the distribution was 56% male and 44% female. At 188 µg/L, 31% of fish were male and 53% female, with the remainder intersex (with testes-ova). At 202 µg/L, 23% were male and 58% female, with the remainder intersex. At 599 µg/L, 93% of the fish were female with the rest undifferentiated, and no males.

In a fish sexual development test conducted as part of an OECD test method validation round (Series on Testing and Assessment No. 141), a skewed sex ratio was observed in fathead minnow exposed to 4-tert-pentylphenol from 0 to 60 dph (60 days exposure). In the control group, fish were 58% female and 40% male, with the remainder sexually undifferentiated. At 93 µg/L 4-tert-pentylphenol, 88% of fish were female, 6% male, and 6% undifferentiated. At 296 µg/L, 75% of fish were female with the rest undifferentiated, and no males. Two additional studies conducted as part of this validation round using zebrafish found similar effects, with evidence of impacted sexual differentiation after 60 days beginning at exposure concentrations of 62 µg/L and 100 µg/L. In two more additional studies conducted in phase 2 of the same validation round, medaka exposed to 4-tert-pentylphenol over 60 and 70 days from the time egg fertilisation had impacted sexual differentiation beginning at exposure concentrations of 294 µg/L and 318 µg/L respectively.

These studies are strong evidence that 4-tert-pentylphenol exerts effects through an endocrine mode of action, as effects upon sexual differentiation are an apical endpoint for an estrogen agonist mode of action (OECD 2004).

Predicted no-effect concentration (PNEC)

A freshwater PNEC for 4-tert-butylphenol of 1 µg/L was derived from the measured fish chronic ecotoxicity endpoint (128d NOEC = 0.01 mg/L) using an assessment factor of 10. This assessment factor was selected as reliable chronic ecotoxicity data are available over 3 trophic levels.

A freshwater PNEC for 4-tert-pentylphenol of 2 µg/L was derived from the measured fish chronic ecotoxicity endpoint (60d NOEC = 0.1 mg/L) using an assessment factor of 50. This assessment factor was selected as reliable chronic ecotoxicity data are available over 2 trophic levels, including the most sensitive trophic level.

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to Australian environmental hazard thresholds is presented below:

Persistence

Not Persistent (Not P). Based on measured degradation study results, chemicals in this group are categorised as Not Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on low measured bioconcentration factors (BCF) in fish, chemicals in this group are categorised as Not Bioaccumulative.

Toxicity

Toxic (T). Based on available ecotoxicity values below 1 mg/L and evidence of adverse endocrine activity, chemicals in this group are categorised as Toxic.

GHS classification of environmental hazard

Based on the available data, 4-tert-butylphenol satisfies the criteria for classification as Acute Aquatic Category 2 (H401) and Chronic Aquatic Category 1 (H410), and 4-tert-pentylphenol satisfies the criteria for classification as Acute Aquatic Category 2 (H401) and Chronic Aquatic Category 2 (H411) under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (UNECE 2017). Chemicals in this group are rapidly degradable with adequate conventional acute and chronic aquatic toxicity data available.

Environmental risk characterisation

Based on the PEC and PNEC values determined above, the following Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of 4-tert-butylphenol and 4-tert-pentylphenol into rivers:

Chemical name	PEC	PNEC	RQ
4-tert-butylphenol	0.1 µg/L	1 µg/L	0.1
4-tert-pentylphenol	0.01 µg/L	2 µg/L	0.005

The predicted concentrations of chemicals in this group in Australian surface waters are below the level of concern (RQ <1) based on standard OECD ecotoxicity test endpoints. The industrial uses of 4-tert-butylphenol and 4-tert-pentylphenol are; therefore, unlikely to pose a significant risk to the environment based on this metric.

The quantitative RQ estimates above are based on PNECs derived from standard OECD ecotoxicity tests and do not consider the observed endocrine related effects of 4-tert-butylphenol and 4-tert-pentylphenol. Many of these effects were observed at substance exposure concentrations similar to the concentrations used in the standard ecotoxicity tests. However, endocrine mediated effects typically occur at distinct life stages of an organism and quantitative analysis of these effects requires specific test methods. At present, there are insufficient data to determine an exposure level unlikely to cause adverse endocrine related effects (PNEC) or to quantify the environmental risks of these effects. Therefore, RQs above may underestimate environmental risks posed by these chemicals.

Uncertainty

This evaluation was conducted based on a set of information that may be incomplete or limited in scope. Some relatively common data limitations can be addressed through use of conservative assumptions (OECD 2019) or quantitative adjustments such as assessment factors (OECD 1995). Others must be addressed qualitatively, or on a case-by-case basis (OECD 2019).

The most consequential areas of uncertainty for this evaluation are:

- There are only limited Australian monitoring data for 4-tert-butylphenol and 4-tert-pentylphenol. The risk profile of 4-tert-butylphenol and 4-tert-pentylphenol may change should Australian monitoring data become available to indicate that chemicals in this group are present in Australia at concentrations significantly different from the predicted concentrations.
- There are insufficient ecotoxicity data to fully characterise the acute and chronic toxicity of this group of chemicals to sediment and soil-dwelling organisms. Additional reliable ecotoxicity data may change the outcome of the evaluation.
- There are insufficient data to fully characterise the risks posed to the environment from the endocrine effects of these chemicals. Further evaluation may be required should additional reliable effects or exposure data become available.

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