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Environmental risk evaluation report: 4-tert-pentylphenol (CAS no. 80-46-6)

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Steve Killeen

Head of Science

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Executive summary

4-*tert*-Pentylphenol (CAS number 80-46-6) belongs to a group of related substances called alkylphenols. These chemicals are of concern because they may cause effects on endocrine systems in wildlife and people. 4-*tert*-Pentylphenol is used as a chemical intermediate in Europe (mainly for phenolic resins), although it is supplied in relatively small amounts. Only two European suppliers are known, and further market information is commercially sensitive. This assessment is the first detailed environmental risk assessment for 4-*tert*-pentylphenol in the public domain. It follows the format of risk assessments set out by the Existing Substances Regulation.

4-*tert*-Pentylphenol is expected to biodegrade relatively quickly in the environment. It is fairly soluble in water, and its octanol–water partition coefficient (log K_{ow}) implies a moderate bioaccumulation potential in fish. The substance is expected to partition mainly to soil and sediment when it is released to the environment. In general, no reliable environmental monitoring data are available, which means that most of the exposure assessment is based on generic industry information and a number of assumptions. Predicted environmental concentrations are likely to be overestimates as a result. However, the releases at one UK site are based on specific information.

A reasonable amount of reliable information is available to assess the environmental hazard potential of 4-*tert*-pentylphenol. It is acutely toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment. 4-*tert*-Pentylphenol is not a persistent, bioaccumulative and toxic (PBT) chemical (since it does not meet the required persistence or bioaccumulation criteria). The predicted no-effect concentration (PNEC) chosen for the freshwater risk assessment is 2 µg/L, based on effects on fish. However, there is some uncertainty in this value, and further investigation of long-term toxicity to fish would be helpful. The PNECs for sediment and soil are derived from the surface water PNEC. The PNEC for predators exposed through food is 4.7 mg/kg, based on mammalian toxicity data for an analogue substance.

Potential risks to the aquatic environment are identified for several parts of the life cycle. Potential risks to wastewater treatment plant and soil are also identified for one specific life cycle step. No risks are expected for air, secondary poisoning of predators or human health following environmental exposure for any stage of the life cycle. Risks for workers and consumers have not been assessed.

In a UK context, there is a potential aquatic risk at a single site. This site is subject to authorisation under pollution control legislation, which offers scope for reducing emissions. The other uses that pose a potential risk are not known to occur in the UK. In any case, the calculations for these are based on default release estimates, and more detailed data on actual emissions (preferably based on measured concentrations) would be needed before risk management decisions could be taken.

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A small amount of confidential information is placed in an annex to this report, which is not available to the general public.

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Preface

The Environment Agency has taken an interest in a group of chemicals called alkylphenols ever since it became known that some can affect the endocrine systems of wildlife. We commissioned a scoping study to review the uses and properties of a large number of these compounds to identify potential priorities for further investigation (EA, 2005a). This led to in-depth reviews of two high tonnage alkylphenols (EA, 2005b, 2007). Pentylphenol (also known as amylphenol) was also identified as a high priority candidate in this study since there is a potential for exposure in the United Kingdom and there were no previous public reviews of hazard or risk.[1] Consequently, the UK Government wanted to provide more information on its potential risks to the environment and to human health following environmental exposure. The substance was included in the UK Co-ordinated Chemicals Risk Management Programme in July 2005 (see http://www.defra.gov.uk/environment/chemicals/ukrisk.htm for further details about this initiative).

The purpose of this report is to identify the properties of this chemical that might lead to environmental or human health concerns. It also investigates the points in its life cycle where risks might be occurring, although the report does not address human health risks following exposure of either workers or consumers. The data collection and peer review processes are described in Appendix 4.

This assessment is based on data provided voluntarily by industry. In general, specific information on uses and process releases is very limited. However, given the nature of the open market, we have assumed that any use of the substance reported in Europe might also take place in the UK, unless there is reliable information to show that this is clearly not the case (e.g. if only a small number of locations are known to use a particular process). Similarly, estimates of pentylphenol releases based on European sources are assumed to be applicable in the UK.

Risk assessments generally use data from tests conducted on the substance itself. However, in this case we have also considered data from laboratory tests on analogue substances (particularly 4-*tert*-butylphenol, which is undergoing a comprehensive risk assessment under Council Regulation (EEC) 793/93, known as the Existing Substances Regulation (ESR)).

The layout of this report follows the format (with a few small modifications) of a risk assessment carried out under the ESR. Readers familiar with such assessments should be able to quickly find the information they are seeking.

Note: Despite the best efforts of the consulted companies and the Environment Agency, the exposure assessment relies on a number of assumptions and so might not be wholly realistic. It is also possible that some other uses of pentylphenol exist that are not known to the Environment Agency or the main suppliers of the substance. The report draws its conclusions based on current knowledge, but the information it contains should be read with care to avoid possible misinterpretations or misuse of the findings. Anyone wishing to cite or quote this report should contact the Environment Agency beforehand.

[1] A hazard evaluation has recently been published following the submission of information under the US EPA HPV Challenge Program (US EPA, 2007c). This has been consulted in the preparation of this report.

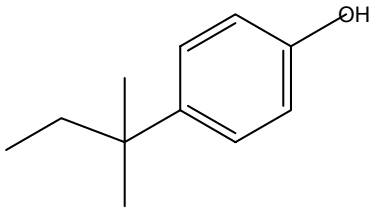
In addition, the possibility of additive or synergistic effects with other alkylphenols has not been considered in this report. Such an approach is more suited to site-specific assessments because of the differences in use pattern of the chemicals involved.

1 General substance information

1.1 Identification of the substance

CAS number	80-46-6
EINECS number	201-280-9
IUPAC name	4-*tert(iary)*-pentylphenol
EINECS name	*p(ara)*-(1,1-dimethylpropyl) phenol
Molecular formula	$C_{11}H_{16}O$
Molecular weight	164.25 g/mole
Structural formula	HO-C_6H_4-C_5H_{11}, where C_6H_4 is a benzene unit substituted at the 1,4- position
SMILES code	CCC(C)(C)c1ccc(O)cc1

Figure 1.1 Structure of 4-*tert*-pentylphenol



(Note: there is no variation in the branching of this substance)

Synonyms (TOXNET, 2005)

1-hydroxy-4-(1,1-dimethylpropyl)benzene
2-methyl-2-*p*-hydroxyphenylbutane
4-*tert*-amylphenol
para- (or *p*-) *tert*-amylphenol
para- (or *p*-) *tert*-pentylphenol
Ucar amyl phenol 4T
p-(alpha,alpha-dimethylpropyl)phenol
Pentaphen

1.1.1 Other isomers

Only one CAS number is used to describe the commercially available product, as indicated above. However, as is often the case with industrial chemicals, several other individual isomers have their own CAS numbers:

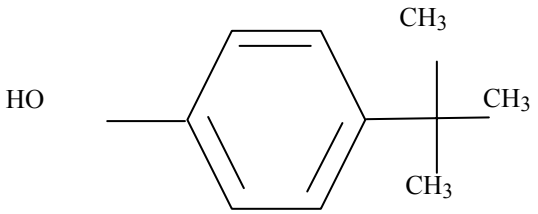
2-pentylphenol (CAS no. 136-81-2; EINECS no. 205-261-6)
3-pentylphenol (CAS no. 20056-66-0; EINECS no. 243-487-7)
4-pentylphenol (CAS no. 14938-35-3; EINECS no. 239-015-4)

None of these substances is identified as being commercially important (i.e. supplied above 10 tonnes/year by a company) according to the European Chemical Substances Information System (ESIS), which is part of the European Chemicals Bureau website (http://ecb.jrc.it/). They are therefore not considered further in this assessment.

1.1.2 Structural analogues

Although data on the chemical and physical properties of 4-*tert*-pentyphenol are best taken from laboratory tests on the substance itself, where there is some uncertainty in a particular result (e.g. because an original study report is unavailable for review) – or where there are no data at all – it can sometimes be useful to consider measurements obtained for similar chemicals. In this case, there are a number of related *para*-substituted alkylphenols, including methyl-, ethyl-, *n*-propyl-, isopropyl-, *n*-butyl-, isobutyl-, *tert*-butyl-, *n*-hexyl-, *n*-heptyl- and *tert*-octylphenols.[2] Detailed risk assessment reports are available for 4-*tert*-butylphenol (CAS no. 98-54-4) and 4-*tert*-octylphenol (CAS no. 140-66-9) (EA, 2005b; SFT, 2007). The former substance is the closest analogue, since it only differs structurally from 4-*tert*-pentyphenol in that it contains one less carbon atom in its alkyl chain. Its structure is provided in Figure 1.2.

Figure 1.2 Structure of 4-*tert*-butylphenol



Appendix 1 contains information for 4-hexylphenol and 4-heptylphenol, although no detailed public risk assessment is available for these substances.

[2] The suffix '*tert'* refers to a tertiary-substituted carbon atom (i.e. with four carbon atoms attached to it); '*n'* refers to a straight alkyl chain with no branching; and 'iso' refers to an alkyl chain that is branched in an unspecified manner.

1.2 Purity/impurities, additives

1.2.1 Purity/impurities

Spectra and original study reports have not been reviewed.

The suppliers' Safety Data Sheets (SDS) state that the commercial substance is more than 98% pure and that 4-*tert*-pentylphenol is the only component (Sasol, 2004; Schenectady, 2005). However, Lorenc *et al*. (2003) report that the main impurities in the crude substance are 2-*tert*-pentylphenol and 2,4-di-*tert*-pentylphenol. The suppliers have confirmed that these two compounds, along with water, may be present in the commercial substance at very low levels (S Mueller & H Certa, pers. comm.).

The substance is assumed to be essentially pure for the purposes of this report. It should be noted that unlike some longer chain alkylphenols (e.g. nonylphenol) there is no variation in branching of the alkyl chain.

1.2.2 Additives

There are no reported additives used to stabilise the substance.

1.3 Physico-chemical properties

The following section provides a summary of the chemical and physical properties of 4-*tert*-pentyphenol. The experimental information was obtained from SDS for the commercial substance (Sasol, 2004; Schenectady, 2005). The original reports were not available for independent evaluation, so the reliability of the data is unclear (e.g. in terms of test substance identity and whether an appropriate test method was followed). The review has therefore been supplemented by comparison with data for 4-*tert*-butylphenol and computer predictions where relevant.

1.3.1 Physical state (at n.t.p.)

4-*tert*-Pentylphenol is a solid, which is usually marketed in the form of a powder, flakes, or briquettes. It is also available in molten form (Lorenc *et al*., 2003).

1.3.2 Melting point

The melting point is stated to be ~93°C (Sasol, 2004; unknown method), 90°C (Schenectady, 2005; unknown method) and 94°C (The Merck Index, 1989). The US EPA's EPI Suite software cites a measured value of 95°C, though no reference is provided (US EPA, 2007a). Lorenc *et al*. (2003) report a melting point of 90°C with no further reference.

These values are similar to the reported melting point of ~100°C for 4-*tert*-butylphenol (SFT, 2007). Although this has a lower molecular weight, the higher melting point may be attributable to crystal structure.

Given the range of measurements, a mid-range value of 93°C is preferred for modelling purposes.

1.3.3 Boiling point

The boiling point is stated to be 256°C (at 1013 hPa; Sasol, 2004; unknown method) or 249°C (Schenectady, 2005; unknown method – the same value is reported by Lorenc *et al*., 2003). The US EPA's EPI Suite software cites a measured value of 262.5°C, though no method or reference is provided (US EPA, 2007a) – the same value is cited by the Merck Index (1989).

The SPARC v4.0[3] model predicts a boiling point of 267°C, with the SMILES code and a melting point of 93°C as the input.

These values are similar to the reported boiling point of 237.5°C for 4-*tert*-butylphenol (SFT, 2007). The lower molecular weight substance boils at a lower temperature, which is as expected.

The mean of the three reported values is 256°C (assumed to be measured at 1013 hPa), and this will be taken to represent the boiling point for the purposes of this assessment.

1.3.4 Relative density

The density is stated to be 0.922 g/cm^3 (at 100°C; Sasol, 2004; unknown method) and 0.962 g/cm^3 (Schenectady, 2005; unknown method). There is no practical consequence for this assessment.

1.3.5 Vapour pressure

Vapour pressure is an important parameter, since it helps to establish the extent to which a substance moves between air and other media (such as water).

1.3.5.1 Measured data

The vapour pressure is stated to be 310 Pa at 100°C (Sasol, 2004; unknown method), 5 mmHg (equivalent to 667 Pa) at 110°C (Schenectady, 2005; unknown method), 0.002 mm Hg (equivalent to 0.27 Pa) at 25°C (Daubert & Danner, 1989; unknown method). The latter value is an extrapolation according to the US EPA's EPI Suite software (US EPA, 2007a).

[3] http://ibmlc2.chem.uga.edu/sparc/

1.3.5.2 Predicted data

A vapour pressure of 0.15 Pa (0.00116 mmHg) at 25°C can be estimated with the MPBPWIN v1.41 model (modified Grain method), based on the melting point of 95°C and a boiling point of 262.5°C from the model's experimental database (US EPA, 2007a). Using the values for melting point and boiling point preferred for this assessment, the same model gives a calculated vapour pressure of 0.23 Pa (0.00175 mmHg). A vapour pressure of 1.04 Pa (0.00783 mmHg) calculated using the same method (presumably using different input terms) is cited in US EPA (2007b).

The SPARC v4.0 model also predicts a low vapour pressure of 3.09×10^{-6} atmospheres (equivalent to 0.31 Pa) at 25°C, with the SMILES code and a melting point of 93°C as the input.

The validity of these predictions is unclear.

1.3.5.3 Data from structural analogues

The vapour pressure of 4-*tert*-butylphenol is reported to be 0.5 Pa at 20°C (SFT, 2007).

1.3.5.4 Selected value

A vapour pressure of 0.27 Pa at 25°C will be assumed for this assessment. This is a measured value, and although the primary reference has not been reviewed, it is taken from a widely used and authoritative source (US EPA, 2007a). It is in close agreement with the predicted values and consistent with the data for a close analogue.

1.3.6 Water solubility

1.3.6.1 Measured data

The water solubility is stated to be 37 mg/L at 20°C (Sasol, 2004; unknown method) and 0.2% (equivalent to 2,000 mg/L) (Schenectady, 2005; unknown method). The EPI Suite software (US EPA, 2007a) cites a measured value of 168 mg/L at 25°C (Yalkowsky & Dannenfelser, 1992; method unknown).

1.3.6.2 Predicted data

Several QSAR estimates have been performed using three software tools (VCCLabs ALOGPS V.2.1,[4] SPARC v4.0 and WSKOW v1.41/WATERNT v1.01 (US EPA, 2007a)) with the SMILES code as the input. The results are presented in Table 1.1.

[4] http://146.107.217.178/lab/alogps/start.html

Table 1.1 Predicted water solubility values for 4-*tert*-pentylphenol

Model	Predictied water solubility	Units	Comment
ALOGpS	160	mg/L	
AB/LogS	100	mg/L	
WSKOW	113.2	mg/L	Using the predicted log K_{ow} of 3.91
	72.3	mg/L	Using a log K_{ow} of 4.03 (see Section 1.3.7) and a melting point of 93°C
WATERNT	417.8	mg/L	Molecular fragments
SPARC	2.19×10^{-5}	Mole fraction	Basis not clear – 'fundamental chemical structure theory'

A water solubility estimate of 141.4 mg/L (at 25°C) can also be made with WSKOWWIN (v1.41) using octanol–water partition coefficient data from 4-*tert*-butylphenol (see Section 1.3.7.3) as the starting point and adding the relevant fragment data.

1.3.6.3 Data from structural analogues

The mean water solubility of 4-*tert*-butylphenol is reported to be 610 mg/L at 20°C (SFT, 2007).

1.3.6.4 Selected value

A water solubility of 168 mg/L at 25°C will be assumed for this assessment. This is a measured value, and although the primary reference has not been reviewed, it is taken from a widely used and authoritative source (US EPA, 2007a). It is in reasonably good agreement with the predicted values and consistent with the data for a close analogue.

1.3.7 *n*-Octanol–water partition coefficient

The *n*-octanol–water partition coefficient (K_{ow}) is a measure of the hydrophobicity of a chemical. It is used to predict environmental partitioning behaviour as well as aquatic toxicity.

1.3.7.1 Measured data

The log K_{ow} is stated to be 4.03 (Schenectady, 2005; method unknown). A robust study summary submitted to the US EPA by this company indicates that this information was 'taken from a literature search covering appropriate databases' by Schultz (1987), and that it was not obtained in accordance with good laboratory practice (GLP) (US EPA, 2007b).

1.3.7.2 Predicted data

Several QSAR estimates have been performed using two software tools (VCCLabs ALOGPS V.2.1 and KOWWIN v1.67 (US EPA, 2007a)) with the SMILES code as the input. The results are presented in Table 1.2.

Table 1.2 Predicted K_{ow} values for 4-*tert*-pentylphenol

Model	Predicted log K_{ow}
ALOGPs	3.92
AB/LogP	3.69
MiLogP	3.49
COSMOFrag	3.05
XLOGP	4.0
KOWWIN	3.91

The reliability of the individual predictions is not known, although the KOWWIN model gives good estimates of log K_{ow} in the range 0–5 (EC, 2003). This analysis suggests that the log K_{ow} should be in the range 3.5–4.0. The geometric mean of the predictions is 3.66.

1.3.7.3 Data from structural analogues

The log K_{ow} of 4-*tert*-butylphenol is reported to be 3.29 (SFT, 2007). Using this value in KOWWIN v1.67 and adding the relevant fragment constant[5] produces an estimated log K_{ow} for 4-*tert*-pentylphenol of 3.78.

1.3.7.4 Selected value

A log K_{ow} of 4.0 will be assumed for this assessment. Although no test report is available for review, this value represents the upper end of the predicted values.

1.3.8 Hazardous physico-chemical properties

Hazardous physico-chemical properties are relevant to this assessment from the point of view of laboratory hazards that might limit testing options, and possible controls that might be required for process equipment (e.g. to exclude air if a substance is pyrophoric).

The flash point is stated to be ~134°C using the DIN 51758 test (Sasol, 2004) and 121°C using the Tag closed cup method (Schenectady, 2005; Lorenc *et al*. (2003) report the same value but with no further details). This is similar to the reported flash point of ~115°C for 4-*tert*-butylphenol (SFT, 2007).

The flammability class is quoted as 'combustible IIIB' (Schenectady, 2005).

The chemical structure of this compound does not suggest that explosive or oxidising properties are likely.

[5] The fragment approach takes the contribution estimated for the additional $–CH_2-$ group in pentylphenol and adds this to the log K_{ow} value for butylphenol.

1.3.9 Other relevant physico-chemical properties

1.3.9.1 Particle size

No information is available on particle size distribution.

1.3.9.2 pKa

The pKa for 4-*tert*-pentylphenol is stated to be 10.4 (Schultz, 1987) and has been predicted to be 10.3 and 10.25 using the ALOGPS V.2.1 and SPARC v4.0 models respectively (using the SMILES code as the input). The substance will therefore be essentially undissociated at normal environmental pH values (5–8). This value is entirely consistent with those of other alkyphenols.

1.3.10 Summary of physico-chemical properties

Table 1.3 summarises the key physico-chemical data used for this assessment.

Table 1.3 Key physico-chemical properties of 4-*tert*-pentylphenol used in the risk assessment

Property	Value	Reference or comment
Molecular weight	164.25 g/mol	-
Melting point	93°C	Middle of measured range
Boiling point	256°C at 101.3 kPa	Mean of measured data
Vapour pressure	0.27 Pa at 25°C	Daubert & Danner (1989)
Water solubility	168 mg/L at 25°C	Yalkowsky & Dannenfelser (1992)
n-Octanol–water partition coefficient (K_{ow})	4.0	Upper limit of predicted values

2 General information on exposure

2.1 Production and import

The European Commission's ESIS database (http://ecb.jrc.it/esis/) lists 4-*tert*-pentylphenol as a low production volume chemical (i.e. supplied in quantities between 10 and 1,000 tonnes/year at least once by a company in 1990–94). Table 2.1 lists the European producers or importers identified in ESIS.

Table 2.1 Producers and importers of 4-*tert*-pentylphenol in the early 1990s

Company	Town	Country
BAKER PETROLITE	Liverpool	UK
CONDEA CHEMIE GMBH	Marl	Germany
HUELS AG	Marl	Germany
ECEM EUROPEAN CHEMICAL MARKETING B.V.	Amsterdam	The Netherlands
SCHENECTADY PRATTELN AG	Pratteln	Switzerland

This source of information is over 10 years old, and does not reflect the current state of the market. Consultation for the purposes of this report has only identified one producer (Sasol Germany GmbH – formerly Hüls AG) and one importer (Schenectady International Inc.) that are still active in the EU market. Further details of the amounts supplied by these companies are provided in a Confidential Annex to this report to avoid revealing commercially sensitive information. There is no known production site in the UK.

Lorenc *et al*. (2003) state that 4-*tert*-pentylphenol is commercially produced by the alkylation of phenol with isoamylene under acidic catalysis. Isoamylene is a mixture of 2-methyl-1-butene and 2-methyl-2-butene, which is produced by dehydration of the corresponding alcohol or backcracking of the corresponding methyl ether. The highest purity isoamylene is available from the backcracking of *tert*-amyl methyl ether (TAME), produced from a C_5 raffinate stream by reaction with methanol under acid catalysis. The substance is purified by fractional distillation. Further details of the production process in the EU are available in the Confidential Annex.

2.2 Uses

2.2.1 Publicly available information

Lorenc *et al*. (2003) provide the following information on uses, although this source may have a North American bias:

- 4-*tert*-Pentylphenol is used to make phenolic resins (novolaks and resoles), which are used in paints and varnishes and as printing ink resins. The ethoxylated novolaks are used as oil field demulsifiers. Because of the high cost of 4-*tert*-pentylphenol, which is related to the high cost of the starting material, many of the resin applications have been reformulated using 4-*tert*-butylphenol.

- The substance is also used as a germicide in cleaning solutions, although it is being replaced by quaternary ammonium salts. Kegley *et al*. (2007) confirm that both the substance and its potassium and sodium salts are antimicrobial or fungicidal active ingredients of several disinfectant products that are currently registered with the US authorities. It appears that some of these products are used in animal husbandry, including the control of highly infectious diseases such as avian influenza (US EPA, 2007d)

- The disulphide derivative of 4-*tert*-pentylphenol is used as a vulcanising agent for the curing of rubber.

The SPIN (Substances in Preparations in Nordic Countries) database (http://195.215.251.229/DotNetNuke/default.aspx) provides data on the use of chemical substances in Norway, Sweden, Denmark and Finland. The information is derived from the Product Registries of the contributing countries. A search of the online database in October 2007 found a number of records up to 2005, but few details are publicly available. Some use in consumer products is indicated, and product categories that are mentioned include 'paint industry', 'cleaning/washing agents', 'conductive agents' and 'non-agricultural pesticides and preservatives'. The tonnages involved appear to be very low.

The ESIS database indicates that certain derivatives may be on the market, and these are summarised in Table 2.2 (this list might not be exhaustive).

Table 2.2 Derivatives of pentylphenol apparently available on the EU market

Substance	CAS no.	EINECS no.
2,2'-Thiobis(4-*tert*-pentylphenol)	98-26-0	202-650-2
4-(1,1-Dimethylpropyl) phenol, sodium salt	31366-95-7	250-595-8
Dithiobis(4-(1,1-dimethylpropyl)-phenol)	32074-74-1	250-915-6
4-(1,1-Dimethylpropyl) phenol, potassium salt	53404-18-5	258-524-2
Pentylphenol, dinitro derivative	71607-47-1	275-688-0

These appear to be of relatively minor commercial importance (e.g. ESIS indicates that they were all supplied in quantities below 10 tonnes/year by companies in the early 1990s).

2.2.2 Suppliers' information on use pattern

Table 2.3 summarises the main uses of 4-*tert*-pentylphenol in the EU identified by the current suppliers, in order of tonnage consumed (phenolic resin manufacture being the most important). Only limited information can be summarised in this report because market data are commercially sensitive for the two suppliers. There appear to have been four main types of use in the EU in recent years, and at least one of these takes place in the UK (at two known sites operated by one company). The use as a synthetic intermediate in phenolic resin manufacture is known to all of the companies with an interest in this substance, although the exact tonnages cannot be stated for reasons of commercial confidentiality. Two site types have been identified for use in resin manufacture; one involves production of ethoxylated resins, some of which are used in oilfield applications. One of the scenarios deals with use as a component of disinfectants, although this no longer appears to be relevant in Europe because of recent legislation (see Section 2.4).

Further details are available in a Confidential Annex to this report.

Table 2.3 Summary of the life cycle stages (LCS) of 4-*tert*-pentylphenol in the EU

Life cycle stage	Comment
1 PRODUCTION	Site-specific, therefore only a selection of the results for this LCS can be presented, to prevent the possibility of back-calculation and breach of commercial confidentiality.
2 SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	
3 SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	
4 CONFIDENTIAL USE 1	
5 CONFIDENTIAL USE 2 FORMULATION	This LCS has formulation and use stages.
5 CONFIDENTIAL USE 2	
6 OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	This is associated with the use of polymers manufactured under LCS 2/3.
7 CONFIDENTIAL USE 3 – FORMULATION	This LCS has formulation, use, service life and disposal stages. The latter two are treated locally, although they are almost equivalent to regional releases.
8 CONFIDENTIAL USE 3 – USE	
9 CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	
10 CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	

2.3 Trends

No data on trends in the use or production of 4-*tert*-pentylphenol are currently available.

2.4 Regulatory **initiatives**

No substance-specific legislative controls currently exist. The use of 4-*tert*-pentylphenol in disinfectants is subject to the Biocidal Products Regulations 2001 (Statutory Instrument 2001/880), which implement the EU Biocidal Products Directive (98/8/EC). Industry has not supported its continued use as an active substance in this application, and so disinfectant products containing it had to be removed from the market by 1 September 2006. There is always a possibility that it may be used again for this purpose in future, but the products would be subject to a detailed review because 4-*tert*-pentylphenol would be treated as a new active substance.

The sites that are known to use 4-*tert*-pentylphenol in the UK are subject to authorisations under the Pollution Prevention and Control (England and Wales) Regulations, 2000. Under this legislation, all installations and mobile plant should be operated in such a way that:

- appropriate preventative measures are taken against pollution, in particular through application of the best available techniques; and
- no significant pollution is caused.

In practice, if releases from a process falling under these Regulations were sufficiently high to cause concern, then release limits would be imposed, or an improvement condition would be set requiring a reduction in releases over an agreed period of time.

4-*tert*-Pentylphenol was considered during the development of the European Commission's strategy on endocrine disruptors. It appeared on an initial list of candidate substances but was not selected for further analysis at that time because SMILES notations were not readily available and therefore QSAR calculations could not be carried out (BKH, 2000). Subsequently a further evaluation was made and this substance was placed in the category 'not HPV, not persistent' or 'no exposure expected' (BKH, 2002).

As of 1 October 2007 4-*tert*-pentylphenol does not appear on the High Production Volume (HPV) Chemical lists of the International Council of Chemical Associations (ICCA) (http://www.iccahpv.com) or the Organisation for Economic Co-operation and Development (OECD) (http://cs3-hq.oecd.org/scripts/hpv/), presumably because it is not supplied at sufficiently high tonnages internationally. A hazard evaluation has been performed under the US EPA HPV Challenge Program (US EPA, 2007b, 2007c). In addition, the US EPA has reviewed the available data for the use of this substance as a disinfectant (US EPA, 2005).

4-*tert*-Pentylphenol has been used as a model test compound in a laboratory intercalibration study with fish organised by the OECD's Validation Management Group for Ecotoxicity Testing. Available results are presented in Section 4.1.1.3.4.

3 Environmental exposure

This assessment has been prepared in accordance with the principles of Council Regulation (EEC) 793/93 (the Existing Substances Regulation or ESR)[6] and the methods laid down in Commission Regulation (EC) 1488/94,[7] which is supported by a technical guidance document or 'TGD' (EC, 2003). The European Union System for the Evaluation of Substances (EUSES) computer program[8] (v2.0.3) implements the TGD models. The EUSES output file for this assessment is confidential because of the information it contains on tonnage and use pattern.

The assessment is generic, representing a *realistic worst case approach* for a hypothetical environment that broadly reflects average European conditions. Further details can be found in the TGD. The assessment is based on estimated sales figures for Europe and some site-specific information. Since these are confidential, the calculations are presented in the Confidential Annex, but they are discussed qualitatively in the report as appropriate.

3.1 Environmental fate and distribution

3.1.1 Atmospheric degradation

No measured data are available. One of the main degradation processes for organic chemicals in the troposphere is the gas-phase reaction with the hydroxyl (OH) radical. Using the chemical structure as the input term, AOPWIN v1.9.1 (US EPA, 2007a) was used to estimate a reaction rate constant with OH radicals of 4.18×10^{-11} cm^3/molec/s. This is equivalent to a rate constant for degradation in air of 1.81 d^{-1}, or a half-life of 9.2 hours (calculated using EUSES).

3.1.2 Aquatic degradation

3.1.2.1 Abiotic degradation

No data are available. However, considering the chemical structure of 4-*tert*-pentylphenol, no significant abiotic degradation mechanisms in water are likely to occur.

3.1.2.2 Biodegradation

The biodegradability of 4-*tert*-pentylphenol has been studied using an aerobic test in an aqueous medium (OECD 301B: CO_2 Evolution Test; BMG, 1999). A copy of the study report has been provided for this review. The concentration of substance used in the test (20 mg/L) was within the measured water solubility and degradation was assessed using both CO_2 evolution and dissolved organic carbon (DOC) measurement. After 28 days 73% of the substance degraded, but only 52% was degraded within the 10-day window. The substance can therefore be described as 'readily biodegradable, failing the 10-day window'. The same conclusion has been drawn for 4-*tert*-butylphenol (SFT, 2007).

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[6] O.J. No L 084, 05/04/1993 p. 0001–0075.

[7] O.J. No L 161, 29/06/1994 p. 0003–0011.

[8] Available from the European Chemicals Bureau, http://ecb.jrc.it/

Using this biodegradation characterisation in the EUSES model gives an estimated rate constant for degradation in regional surface water of 0.0139 d^{-1} (at 12°C), equivalent to a half-life of 50 days. Similarly, estimated half-lives for biodegradation (at 12°C) in aerated and bulk sediment are 900 and 9,000 days respectively.

3.1.3 Degradation in soil

No experimental data are currently available. The estimated rate constant for degradation in bulk soil in the EUSES model (based on the characterisation as 'readily biodegradable, failing the 10-day window') is 7.7 x 10^{-3} d^{-1} (at 12°C), equivalent to a half-life of 90 days.

3.1.4 Adsorption

The organic carbon–water partition coefficient (K_{oc}) is an important parameter because it is used to estimate other environmental partitioning coefficients. No measured values are available for 4-*tert*-pentylphenol, but the K_{oc} can be predicted using quantitative structure–activity relationships (QSARs). The most commonly used models rely on the log K_{ow} as the input, and in this case the QSAR recommended by the TGD for phenols has been used, as implemented in the EUSES 2.03 program. The resulting adsorption coefficients used in the risk assessment are shown in Table 3.1.

Table 3.1 Adsorption coefficients used in the environmental risk assessment

Partition coefficient	Symbol	Values used
Organic carbon–water partition coefficient	Koc	2,300 L/kg
Solids–water partition coefficient for soil	Kp_{soil}	46 L/kg
Solids–water partition coefficient for sediment	Kp_{sed}	120 L/kg
Solid–water partition coefficient for suspended matter	Kp_{susp}	230 L/kg
Soil–water partition coefficient	$K_{soil\text{-}water}$	69 m^3/m^3
Sediment–water partition coefficient	$K_{sed\text{-}water}$	58 m^3/m^3
Suspended matter–water partition coefficient	$K_{susp\text{-}water}$	58 m^3/m^3

Given that the log K_{ow} used for the estimate (4.0) might be an upper limit[9] (see Section 1.3.7), the K_{oc} has also been predicted using molecular connectivity indices for comparison (these are based on molecular structure only). The predicted K_{oc} is 3,799 L/kg using the PCKOCWIN v1.66 model (US EPA, 2007a) and SMILES input. The accuracy of the prediction is unknown, but it is very similar to the value in Table 3.1.

A K_{oc} of 2,380 L/kg has therefore been used for the risk assessment, but the potential influence of different K_{oc} values is discussed further in Section 5.

[9] The geometric mean predicted log K_{ow} (3.7) is equivalent to a K_{oc} of 1,540 L/kg using the phenol QSAR provided in the TGD.

3.1.5 Volatilisation

Volatilisation from surface water is modelled by the Henry's Law constant (HLC).

A measured value is not available. The HLC can be estimated from the vapour pressure, molecular weight and water solubility of the substance using the equation provided in the EC (2003). The HLC estimated using the data from Table 1.3 is 1.02 $Pa.m^3$/mol. This value indicates a moderate preference for water compared to air, and hence a low rate of volatilisation from surface water to air (e.g. in a sewage treatment plant).

For comparison, a HLC of 0.19 $Pa.m^3$/mol can also be estimated using the HENRYWIN v3.10 model's 'bond' method (US EPA, 2007a) based on chemical structure alone. EC (2003) notes that this program is useful for estimating the HLC of highly miscible or highly soluble compounds.

A HLC of 1.02 $Pa.m^3$/mol will be used in this assessment.

3.1.6 Precipitation

The vapour pressure of 4-*tert*-pentylphenol (see Section 1.3.5) is relatively low, and so it is unlikely to enter the atmosphere in large amounts as vapour (except perhaps at elevated temperatures). Once in the atmosphere, the K_{oc} (see Section 3.1.4) suggests that there will be some adsorption to particulates, whereas the HLC (see Section 3.1.5) indicates that the substance prefers to partition to water. It is therefore anticipated that some (but not the majority) of the volatilised substance would be washed back to earth by rain, either in water or adsorbed to particulates.

3.1.7 Environmental distribution

Fugacity modelling indicates how a substance may be distributed in the environment following a release to a specific compartment (air, water, sediment or soil). The potential environmental distribution of 4-*tert*-pentylphenol has been assessed using a generic level III, four-compartment fugacity model (EQC v2.02[10]) that is available for use within the OECD HPV programme. The reaction half-lives in environmental compartments have been set at rates generated by EUSES for the region. The model was run four times with a nominal release rate (entirely to air, water or soil, and equally to all three). The proportions of the released substance in each compartment at steady state are given in Table 3.2. No inflow from outside the modelled area (the whole EU) has been included.

10 Model available from http://webdomino1.oecd.org/comnet/env/models.nsf

Table 3.2 Fugacity modelling results (per cent distribution at steady state)

Compartment	Release to			
	air	water	soil	air:water:soil equally
Air	66.2	0.02	0	2.0
Water	6.3	68.7	0.01	6.3
Sediment	0.7	31.3	0	2.9
Soil	31.7	0.01	99.99	88.8

These results indicate that emissions to air are expected to substantially remain in air, with some precipitation to soil. Emissions to water are expected to mostly remain in the water column, but with some partitioning to sediment. Emissions to soil are expected to remain in soil. There is very little movement between soil and water, because transfer via the air compartment is very slow.

The SIMPLETREAT model used in EUSES estimates the fraction of a substance entering a standard wastewater treatment plant (WWTP) that will be directed to air, water and sludge. Using the physico-chemical, adsorption and degradation properties described in the preceding sections, the fractions for 4-*tert*-pentylphenol are as follows:

To air	0.6%
To water	26.7%
To sludge	18.4%
Degradation	54.2%

3.1.8 Aquatic bioaccumulation

The fish bioconcentration factor (BCF) is a measure of the bioaccumulation potential of a substance in aquatic wildlife. It is used to predict concentrations in fish for both the secondary poisoning and indirect human exposure assessments, and also as part of the PBT assessment (see Section 4.5.2).

3.1.8.1 Measured data

No experimental data for bioconcentration are available.

3.1.8.2 Predicted data

A fish BCF of 501 L/kg may be estimated from the log K_{ow} (4.0) using the QSAR recommended in the TGD[11]. A slightly lower BCF of 240 L/kg can be estimated from the same log K_{ow} using the BCFWIN v2.17 model (US EPA, 2007a).

These values suggest a modest potential for 4-*tert*-pentylphenol to bioconcentrate. In mammals, phenolic compounds are rapidly glucuronidated or sulphated, followed by excretion via the urine or faeces (see Section 4.4.1.1). The same principal metabolic pathways occur in both mammals and fish, so the predicted fish BCF of ~500 L/kg is possibly an overestimate. However, studies have shown that a range of alkylphenols may accumulate in fish bile to higher levels than might be expected from the K_{ow} (e.g. Larsson *et al*., 1999; Gibson *et al*., 2005).

[11] $\log BCF_{fish} = 0.85 \times \log K_{ow} - 0.70$

3.1.8.3 Data from structural analogues

A measured fish BCF of 120 L/kg was selected as a worst case for 4-*tert*-butylphenol (SFT, 2007). This is very close to the predicted BCF using the TGD QSAR and a log K_{ow} value of 3.29.

Sundt & Baussant (2003) investigated the uptake, tissue distribution and elimination of a linear analogue, 4-*n*-pentylphenol, in Atlantic cod (*Gadus morhua*) using both dietary and seawater exposures. Although this study does not meet formal test guideline criteria (e.g. too few fish were used and no information is given about controls), it is summarized in some detail here as it provides useful comparative information.

The same design and sampling procedure was used for both exposure routes. At the start of the experiment, 17 juvenile fish (30 ± 15 g) were placed in 50 L aquaria (13 individuals for the kinetics study plus four extra fish). Six large fish (800 ± 100 g) were held in 250 L tanks for tissue distribution studies. The experiment lasted for 16 days, with 8 days of exposure and 8 days of elimination. A continuous water flow was maintained, at 0.5 and 3.5 L/ min for the small and large fish respectively. Natural seawater was directly pumped from an inlet at 80 metres depth and sand-filtered before supply to the exposure system. The seawater temperature was 11±1°C throughout the experiment. The test substance was tritium-labelled (14 Ci/mmol, radiochemical purity of 95%).

A dose in food corresponding to 5 µg/kg fish was administered daily in the dietary study. For the juvenile fish, commercial fish food pellets (14% fat) were soaked in a 1:10 mixture of radiolabelled test substance and fish liver oil; for the larger fish, raw shrimps were injected with the same mixture. To avoid unfavourable taste affecting appetite, the ration was kept at room temperature for 5 minutes to evaporate some of the acetone prior to feeding. The daily ration of feed was 1% of total body mass of fish left in the tanks (based on food consumption estimated prior to the experiment). The same regime (but with uncontaminated feed) was used for the elimination period. To ensure that all the feed given was ingested, feeding was inspected visually.

For the water exposure experiment, a 2 L stock solution was prepared by mixing radiolabelled test substance in acetone with non-radioactive substance in an appropriate amount to reach a final nominal seawater concentration in the test system of 0.008 µg/L. The final acetone concentration was kept at a maximum level of 30 mg/L. Juvenile fish were fed commercial fish food pellets and large fish were fed shrimps using the same regime as the one described for the dietary study during the whole duration of the experiment.

Concentrations of test substance in both fish and seawater were estimated using liquid scintillation counting (no information is given about how the concentration in food was measured – presumably it is a nominal value).

Three fish replicates (i.e. one fish from three different aquaria) were sampled for kinetic analyses at 0, 6, 12, 24, 48, 96 and 192 hours for both dietary and waterborne exposures. Three fish replicates (all from one tank) were also sampled for tissue distribution analysis at the end of the exposure period (day 8) and at the end of the elimination period (day 16). Each fish was analysed separately. They were first rinsed and then weighed. Liver was analysed separately from the rest of the body tissues (“carcass”). Gut was removed from all fish prior to homogenisation of the carcass. The analytical results of the two samples (liver and carcass) were finally added together to give a weighted body burden (without

gut). Data were expressed as the mean of the three replicates (both seawater and body tissues) ± standard deviation.

A first-order kinetic model was used to estimate uptake and elimination rates in the fish. Despite the continuous flow of seawater, a reduction of seawater concentration was observed with time (the rate constant for this decline was 0.15 day^{-1}), which required the use of a correction term. For the water exposure experiment, uptake occurred relatively rapidly and the maximum body burden of 0.6 µg/kg was achieved after 2 days of exposure (followed by a decline to around 0.35 µg/kg by the end of the exposure period, which suggests a delay in induction of detoxification enzymes). Initial elimination from body tissues was also rapid (the elimination half-life was 15 hours) and 'background' levels were reached after 2 days (it is not stated what these were). The maximum BCF after 2 days of exposure was 107 L/kg (based on kinetic modelling). It should be noted that the analysis would have included radioactive metabolites, so this value may overestimate the overall accumulation of the parent compound.

The same pattern of uptake and elimination was observed in the dietary study, although tissue levels were much lower (the absorption efficiency was estimated to be 8%). Tissue distribution was also similar in both experiments: most of the radioactivity was found in the bile and gastro-intestinal system, with very little in the liver and other internal organs.

The predicted BCF for linear 4-pentylphenol will be the same as for the branched commercial substance (since the estimate is based on the same log K_{ow} value of 4.0). These results therefore suggest that the TGD QSAR equation is conservative for this type of compound.

3.1.8.4 Selected value

The estimated BCF of ~500 L/kg for 4-*tert*-pentylphenol is a conservative value to use for the risk assessment.

3.1.9 Terrestrial bioaccumulation

No measured data are available. An earthworm BCF of 120 L/kg wet weight is predicted using the log K_{ow}-based QSAR given in the TGD.

3.1.10 Summary of environmental fate and distribution

The available data indicate that 4-*tert*-pentylphenol is relatively involatile and moderately soluble in water. It is expected to adsorb fairly strongly to organic matter in soils, sediments and sewage sludges. Degradation processes within these media and air are predicted to be reasonably rapid. If the substance were released directly to the atmosphere, much of it would remain in that compartment (most likely associated with particulate matter). If released to water or soil most of it would stay in the compartment into which it was released.

The potential for bioaccumulation in both aquatic and terrestrial organisms is predicted to be moderate (a fish BCF of ~500 L/kg has been selected as a reasonable worst case).

3.2 Environmental releases

Estimates of releases have been made based on the current supply volume that has been established through consultation with the main suppliers for the purposes of this report. Apart from specific information available for the German production site and one UK site, most releases are default values from the TGD or certain emission scenario documents. Further details are provided in the Confidential Annex to this report, to avoid revealing commercially sensitive information.

3.3 Environmental concentrations

In the following discussion, the 'local' environment is considered to be an area close to a site of release (e.g. an industrial facility). The 'region' represents a highly industrialised area, 200 km $\times$ 200 km in area, with 20 million inhabitants. The continental environment is the size of the EU and is generally used to obtain 'background' concentrations of the substance. It is not possible to deduce tonnage data from the predicted environmental concentration (PEC) values presented in this report because no information is given about the regional tonnage or the site size used in the model. The PECs in the following tables are rounded to two significant figures.

3.3.1 Aquatic compartment (surface water, sediment and wastewater treatment plant)

3.3.1.1 Freshwater concentrations

The predicted environmental concentrations for water local to the point of release (PEC_{local}) are calculated using the environmental releases mentioned in Section 3.2 and the equations set out in Chapter 3 of the TGD (EC, 2003). Essentially, concentrations are estimated in sewage effluent from a 'standard' WWTP for each life cycle step, and the concentration in the receiving water is calculated by assuming a default dilution factor of 10. The PEC_{local} is made up of:

- a local water concentration (C_{local}) resulting from the relevant process emission followed by re-distribution in a WWTP and dilution of the effluent in a river by a factor of 10; and

- a background concentration that results from emissions in the regional environment ($PEC_{regional}$). This regional PEC is itself a result of direct emissions from industrial processes using the substance, and diffuse emissions as a consequence of the use of end products.

The PEC for sediment can be derived from the PEC_{local} for surface water using the suspended matter–water partitioning coefficient, assuming equilibrium partitioning.

PECs for WWTP are based on influent concentrations arising from direct releases.

Table 3.3 shows local PECs for surface freshwater, WWTP and freshwater sediments.

Table 3.3 Local PECs in the freshwater aquatic environment during an emission episode

LCS	Description	Local PEC in surface freshwater, mg/L	PEC for WWTP micro-organisms, mg/L	Local PEC in freshwater sediment, mg/kg wet wt
1	PRODUCTION	4.9×10^{-5}	*	2.5×10^{-3}
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	0.018	*	0.91
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	1.4×10^{-3}	0.014	0.070
4	CONFIDENTIAL USE 1	0.27	2.7	14
5	CONFIDENTIAL USE 2 FORMULATION	2.3×10^{-4}	1.9×10^{-3}	0.012
5	CONFIDENTIAL USE 2	6.5×10^{-4}	6.1×10^{-3}	0.033
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	1.8×10^{-4}	1.4×10^{-3}	8.9×10^{-3}
7	CONFIDENTIAL USE 3 – FORMULATION	6.1×10^{-5}	2.1×10^{-4}	3.1×10^{-3}
8	CONFIDENTIAL USE 3 – USE	4.2×10^{-5}	2.0×10^{-5}	2.1×10^{-3}
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	4.0×10^{-5}	1.7×10^{-6}	2.0×10^{-3}
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	4.2×10^{-5}	1.7×10^{-5}	2.1×10^{-3}

Note: LCS – life cycle stage
***Not shown for reasons of confidentiality.**

Life cycle stages 2 and 4 lead to higher predicted concentrations than the other stages. The regional PECs for surface water and sediment are 4.0×10^{-5} mg/L and 3.4×10^{-3} mg/kg wet weight respectively. No data are available on measured concentrations of 4-*tert*-pentylphenol in freshwaters or sediments.

3.3.1.2 Marine concentrations

Marine compartment exposure to 4-*tert*-pentylphenol has been estimated using generic default scenarios, apart from life cycle stage 2, which is site-specific. The defaults assume that a release of effluent containing the substance direct to marine water could occur without any treatment in a municipal wastewater treatment plant. Table 3.4 shows local PECs for seawater and marine sediments.

Table 3.4 Local PECs in the marine aquatic environment during an emission episode

Life cycle stage	Description	Local PEC in marine surface water, mg/L	Local PEC in marine sediment, mg/kg wet wt
1	PRODUCTION	*	*
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	1.8×10^{-4}	9.6×10^{-3}
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	5.0×10^{-4}	0.025
4	CONFIDENTIAL USE 1	0.010	5.0
5	CONFIDENTIAL USE 2 FORMULATION	7.3×10^{-5}	3.7×10^{-3}
5	CONFIDENTIAL USE 2	2.3×10^{-4}	0.012
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	5.4×10^{-5}	2.7×10^{-3}
7	CONFIDENTIAL USE 3 – FORMULATION	1.1×10^{-5}	5.9×10^{-4}
8	CONFIDENTIAL USE 3 – USE	4.4×10^{-6}	2.2×10^{-4}
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	3.7×10^{-6}	1.9×10^{-4}
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	4.3×10^{-6}	2.2×10^{-4}

Note: *These two PECs are irrelevant for this part of the life cycle since the only known production site is not located at the coast.

Life cycle stage 4 (confidential use 1) is associated with the highest predicted concentrations in seawater and sediment. No data are available on measured concentrations of 4-*tert*-pentylphenol in marine waters and sediments.

3.3.2 Terrestrial compartment

3.3.2.1 Estimated soil concentrations

The TGD method takes into account direct releases to soil, application of sewage sludge containing the chemical and atmospheric deposition. No direct releases to soil are expected in this case, and atmospheric deposition is likely to make a relatively small contribution in view of the low releases to air. The major contribution to soil PECs is therefore from the spreading of sewage sludge.

Different soil PECs are calculated depending on the protection goal. These vary in terms of the depth of soil considered, and the duration and/or route of exposure. Sludge application is assumed to occur once a year for 10 years. The concentration in soil is then calculated at either 30 or 180 days after the last application of sludge (the 30-day average is used in the risk characterisation for soil organisms; the 180-day average is used to estimate exposure of animals and humans through the food chain).

Table 3.5 shows local PECs for agricultural soils and the pore water in these soils.

Table 3.5 Local PECs in the terrestrial environment

Life cycle stage	Description	Local PEC in agricultural soil (30-d average), mg/kg wet wt	Soil pore water concentration, mg/L
1	PRODUCTION	4.8×10^{-4}	7.3×10^{-6}
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	0.055	8.2×10^{-4}
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	0.032	4.7×10^{-4}
4	CONFIDENTIAL USE 1	6.3	0.094
5	CONFIDENTIAL USE 2 FORMULATION	4.4×10^{-3}	6.6×10^{-5}
5	CONFIDENTIAL USE 2	0.014	2.1×10^{-4}
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	3.2×10^{-3}	4.7×10^{-5}
7	CONFIDENTIAL USE 3 – FORMULATION	4.9×10^{-4}	7.4×10^{-6}
8	CONFIDENTIAL USE 3 – USE	4.8×10^{-5}	7.3×10^{-7}
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	5.1×10^{-6}	8.6×10^{-8}
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	4.2×10^{-5}	6.3×10^{-7}

At the regional level the soil concentration in unpolluted or 'natural' soil is used as the background concentration, to avoid double counting of application through sludge. In this case, the regional natural soil PEC is 1.0×10^{-6} mg/kg wet weight.

Life cycle stages 2 to 5 are associated with the highest predicted soil concentrations of 4-*tert*-pentylphenol, with highest pore water concentrations predicted for life cycle stage 4. The spreading of WWTP sludge onto agricultural soil has not been confirmed for any specific site, and it is possible that some other form of waste treatment is used.

3.3.2.2 Measured soil environmental concentrations

No data are available on measured concentrations of 4-*tert*-pentylphenol in soils.

3.3.3 Atmospheric compartment

Local PECs for air have been estimated for each use pattern using EUSES, and are all significantly less than 1 µg/m^3 (they range from 10^{-5} to 10^{-8} mg/m^3). No measured data are available.

3.3.4 Food chain exposure

If a substance accumulates in the food chain, it might reach a concentration in food that could cause toxic effects in a predator that eats that food. This is referred to as secondary poisoning. PECs for fish-eating predators have been calculated with EUSES using a BCF value of 500 L/kg, a default biomagnification factor of 1 (in accordance with the TGD recommendation for a substance with a BCF below 2,000 L/kg) and the estimated PECs for surface or marine water and soil. Half of the dietary intake is assumed to come from local and half from regional sources, to take account of the fact that some species forage for food over a wide area. The PECs are shown in Table 3.6.

Table 3.6 PECs for secondary poisoning

LCS	Description	PEC, mg/kg wet weight			
		Freshwater fish eaten by predators	Marine fish eaten by predators	Fish-eating marine top predators	Earthworms eaten by predators
1	PRODUCTION	**0.022**	-[a]	-[a]	**4.6×10^{-4}**
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	**1.3**	**0.015**	**4.5×10^{-3}**	**0.047**
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	**0.080**	**0.024**	**6.2×10^{-3}**	**0.027**
4	CONFIDENTIAL USE 1	**19**	**6.8**	**1.4**	**5.3**
5	CONFIDENTIAL USE 2 FORMULATION	**0.053**	**0.014**	**4.2×10^{-3}**	**3.8×10^{-3}**
5	CONFIDENTIAL USE 2	**0.10**	**0.033**	**8.0×10^{-3}**	**0.012**
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	**0.053**	**0.014**	**4.2×10^{-3}**	**2.7×10^{-3}**
7	CONFIDENTIAL USE 3 – FORMULATION	**0.021**	**2.2×10^{-3}**	**1.9×10^{-3}**	**4.6×10^{-4}**
8	CONFIDENTIAL USE 3 – USE	**0.020**	**1.9×10^{-3}**	**1.8×10^{-3}**	**8.8×10^{-5}**
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	**0.020**	**1.8×10^{-3}**	**1.8×10^{-3}**	**5.2×10^{-5}**
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	**0.021**	**2.0×10^{-3}**	**1.9×10^{-3}**	**8.2×10^{-5}**

Note: LCS – life cycle stage

a -These two PECs are irrelevant since the production site is inland.

The highest concentrations for all routes are associated with life cycle stage 4 (confidential use 1). No measured data are available for comparison.

3.4 Human exposure

Only exposure via the environment is considered for the purposes of this assessment. Concentrations in air, drinking water and human foodstuffs are modelled following release to surface water or agricultural soil after municipal wastewater treatment. A wider assessment of human exposure should also consider occupational and consumer exposures.

3.4.1 Estimated daily intake

No data are available on measured 4-*tert*-pentylphenol levels in human diets in Europe. The exposure to humans via environmental routes has therefore been estimated using EUSES, and the results for the worst case scenario (life cycle stage 4) are given in Table 3.7.

Table 3.7 Estimated worst case daily human intake values

Route of intake	Predicted concentration	Estimated daily dose (mg/kg bw/d)	Fraction of overall exposure
Fish	37 mg/kg	**0.061**	**0.55**
Root crops	8.6 mg/kg	**0.047**	**0.42**
Leaf crops	0.019 mg/kg	**3.2×10^{-4}**	**2.9×10^{-3}**
Drinking water	0.094 mg/L	**2.7×10^{-3}**	**0.024**
Air	2.5×10^{-6} mg/m^3	**7.3×10^{-7}**	**6.5×10^{-6}**
Meat	1.6×10^{-3} mg/kg	**7.0×10^{-6}**	**6.3×10^{-5}**
Milk	5.1×10^{-4} mg/kg	**4.1×10^{-6}**	**3.7×10^{-5}**
Total local daily dose	-	**0.11**	-

Exposure via consumption of fish and root crops are of a similar magnitude and dominate the other routes. For all other local scenarios the total daily intake is estimated to be less than ~5×10^{-3} mg/kg/d. The regional scenario leads to a total daily intake of 3.5×10^{-5} mg/kg/d.

4 Effects assessment

The following sections summarise the available (eco)toxicity data for 4-*tert*-pentylphenol. Original test reports or journal articles have been reviewed and the reliability of each study is indicated by the relevant Klimisch code[12] (Klimisch *et al*., 1997):

1. Reliable without restrictions
2. Reliable with restrictions
3. Not reliable
4. Not assignable

Most of the ecotoxicity data for 4-*tert*-pentylphenol submitted under the US HPV Challenge Program were predicted values only (HERTG, 2006; US EPA, 2007b, 2007c).

Some of the tests were conducted using metal salts. Since 4-*tert*-pentylphenol is a very weak acid (see Section 1.3.9.2), the anion would be expected to convert rapidly back to the parent phenol in normal test media. Ecotoxicity data for the salts are therefore assumed to be representative for the parent substance itself.

4.1 Aquatic compartment (including sediment)

4.1.1 Toxicity to fish

Reviewed toxicity data for freshwater fish species exposed to 4-*tert*-pentylphenol are summarised in Tables 4.1 and 4.2.

4.1.1.1 Acute toxicity to freshwater species

Good quality acute fish tests with 4-*tert*-pentylphenol have been performed with fathead minnow (*Pimephales promelas*) (Holcombe *et al*., 1984; Geiger *et al*., 1985; Broderius *et al*., 1995[13]), common carp (*Cyprinus carpio*) (Gimeno *et al*., 1998a), rainbow trout (*Oncorhynchus mykiss*) (Davoren & Fogarty, 2005) and medaka (*Oryzias latipes*) (Hagino *et al*., 2001). The most sensitive results are a 96-h LC_{50} of 1 mg/L and a 96-h survival NOEC of 0.18 mg/L reported for *O. mykiss* (Davoren & Fogarty, 2005).

12 Studies were also scored with the more detailed Australasian Ecotoxicology Database system proposed by Hobbs *et al*. (2005). An example is given in Appendix 2, and further details are available on request.

13 Further fathead minnow LC_{50} of 16 mg/L is cited as Russon *et al*. (1997) by US EPA (2005), but no information was available on the test parameters. This reference has not been checked for the purposes of this report.

Table 4.1 Acute toxicity of 4-*tert*-pentylphenol to freshwater fish

Species	Chemical tested	Age/ size	Static/ flow-through	Test conc. meas. ?	Temp. (°C)	Dissolved oxygen (mg/L)	Hardness (mg $CaCO_3$/L) or salinity (‰)	pH	Endpoint & concentration (mg/L)		Reference	Validity & comments
Pimephales promelas (fathead minnow)	4-*tert*-pentylphenol (≥98% purity)	102 mg	Flow-through	Y	26.4	7.4	44.9	6.9–7.7	24h LC_{50} 48h LC_{50} 96h LC_{50}	3.17 2.58 2.50	Holcombe *et al*., 1984	KC: 1
	4-*tert*-pentylphenol (>95% purity)	26–34 days old	Flow-through	Y	25	Not stated	45	7.8	96h LC_{50}	2.59	Geiger *et al*., 1985; Broderius *et al*., 1995	KC: 1
Cyprinus carpio (common carp)	4-*tert*-pentylphenol (>99% purity)	0.5–1.1 g	Static	Y	25	4–6	210	7.6	96h LC_{50} NOEC	1.6 1.3	Gimeno *et al*., 1998a	KC: 2 Controls and exposures were not replicated.
Oncorhynchus mykiss (rainbow trout)	4-*tert*-pentylphenol sodium salt (purity not stated)	0+ fry	Static	N	15	>60% saturation	Not stated	7.2	96h LC_{50} NOEC	1.0 0.18	Davoren & Fogarty, 2005	KC: 2 Test concentrations were not confirmed analytically.
Oryzias latipes (medaka)	4-*tert*-pentylphenol (purity not stated)	Adult fish	Static	Y	25	Not stated	Not stated	Not stated	96h LC_{50}	2.6	Hagino *et al*., 2001	KC: 2 Controls and exposures were not replicated.

Note: KC = Klimisch code

Table 4.2 Chronic toxicity of 4-*tert*-pentylphenol to freshwater fish

Species	Chemical tested	Age/ size	Static/ flow-through	Test conc. meas. ?	Temp. (°C)	Dissolved oxygen (mg/L)	Hardness (mg $CaCO_3$/L) or salinity (‰)	pH	Endpoint & concentration (mg/L)		Ref.	Validity & comments
Oryzias latipes (medaka)	4-*tert*-pentylphenol (99.7% pure)	Two generations (101-d F_0, 61-d F_1), starting with fertilised eggs	Flow-through	Y	24	Not stated	44–61	7.2–7.6	F_0 60-d survival & growth NOEC	0.402	Seki *et al*., 2003	KC: 1
									F_0 abnormal sex differentiation NOEC	0.1		
									F_0 vitellogenin induction NOEC	<0.051		
									F_0 reproductive impairment NOEC	0.1		
									F_1 length NOEC	0.1		
									F_1 sex ratio NOEC	0.1		
	4-*tert*-pentylphenol (purity not stated)	Newly hatched	Flow-through	Y	24.2–25.1	4.8–7.8	Not stated	7.3–7.9	28-d sex-reversal NOECs for male 2^0 sexual characteristics:		Hagino *et al*., 2001	KC: 2 Controls and exposures were not replicated.
									- Dorsal fin length	0.01		
									- Anal fin length	0.01		
									- Papillary processes on anal fin	0.001		
									- Differentiation of male testes into ovaries	0.001		
	4-*tert*-pentylphenol (99.7% pure)	Eggs to 60 days post-hatch	Flow-through	Y	24 ± 1	Not stated	44–61	7.2–7.6	Morphological sex-reversal observed in XY fish exposed to 4-*tert*-pentylphenol. Complete inhibition of $P450_{11\beta}$ mRNA expression in gonads of sex-reversed XY fish at 60-d post-hatch	≥ 0.238	Yokota *et al*., 2005	KC: 1

Note: KC = Klimisch code

Table 4.2 (cont.)

Species	Chemical tested	Age/ size	Static/ flow-through	Test conc. meas. ?	Temp. (°C)	Dissolved oxygen (mg/L)	Hardness (mg $CaCO_3$/L) or salinity (‰)	pH	Endpoint & concentration (mg/L)		Ref.	Validity & comments
Cyprinus carpio (common carp)	4-*tert*-pentylphenol (purity not stated)	50-day-old fish	Inter-mittent flow-through	Not stated	Not stated	Not stated	Not stated	Not stated	Percentage oviduct NOEC	0.1	Gimeno *et al*., 1996	KC: 2 No data on test medium, replication or chemical analysis.
									Number of primordial germ cells NOEC	0.32		
	4-*tert*-pentylphenol (>99% pure)	Fertilised eggs, yolk sac larvae, larvae, or fingerlings of a genetically male population	Semi-static	Y	Not stated	Measured but not reported	120	8–8.2	Formation of oviducts in male fish and reduced number of primordial germ cells in gonads	< 0.07	Gimeno *et al*., 1997	KC: 2 Only a single concentration tested.
	4-*tert*-pentylphenol (>99% pure)	210 days post-hatch (22 ± 0.44 g)	Flow-through	N	25 ± 1	>6	Not stated	7.6 ± 0.2	90-d NOECs:		Gimeno *et al*., 1998b	KC: 2 Controls and exposures were not replicated. Concentrations were not confirmed analytically.
									Vitellogenin induction	0.32		
									Weight and viscerosomatic index[1]	>1.0		
									Gonadosomatic index	<0.032		
									Spermatocrit	0.32		
									Testes histometry (diameter of seminiferous lobules)	<0.032		
	4-*tert*-pentylphenol (>99% pure)	50 days post-hatch (1.3–1.7 g)	Inter-mittent flow-through	Y	25 ± 0.8	4–8	210	7.6 ± 0.4	Growth NOEC	>0.256	Gimeno *et al*., 1998a	KC: 2 Controls and exposures were not replicated.
									Reproductive tract development	<0.036		
									Primordial germ cell NOEC	<0.036		
									Vitellogenin induction NOEC	0.09		

Species	Chemical tested	Age/ size	Static/ flow-through	Test conc. meas. ?	Temp. (°C)	Dissolved oxygen (mg/L)	Hardness (mg $CaCO_3$/L) or salinity (‰)	pH	Endpoint & concentration (mg/L)		Ref.	Validity & comments
	4-*tert*-pentylphenol (99% pure)	Cultured hepatocytes	Semi-static	N	24	No data	Not stated	No data	96-h vitellogenin induction NOEC	3.285	Smeets *et al*., 1999	KC: 2 Concentrations were not confirmed analytically, statistical methods were not reported.

Note: KC = Klimisch code

Table 4.2 (cont.)

Species	Chemical tested	Age/ size	Static/ flow-through	Test conc. meas. ?	Temp. (°C)	Dissolved oxygen (mg/L)	Hardness (mg $CaCO_3$/L) or salinity (‰)	pH	Endpoint & concentration (mg/L)		Ref.	Validity & comments
Pimephales promelas (fathead minnow)	4-*tert*-pentylphenol (>98% pure)	Embryos (24-h post-fertilisation)	Flow-through	Y	25 ± 1	>70% ASV	≥ 200	7.5 ± 0.5	Larval survival NOEC	0.56	Panter *et al*., 2006	KC: 1 Test duration <107 days post-hatch
									Wet weight and standard length NOEC	0.56		
									Female condition factor	<0.056		
									Plasma vitellogenin induction NOEC	0.56		
									Male secondary sexual characteristics NOEC	0.56		
									Gonadosomatic index NOEC	0.18		
									Gonadal sex of fish NOEC	0.18		
									Gonadal attachments NOEC	0.056		
									Liver and kidney histology NOEC	0.56		
	4-*tert*-pentylphenol (>97% pure)	45–100 days post-hatch (150 ± 30 g)	Flow-through	Y	25 ± 1	60–100% ASV	≥ 200	6.2–9	21-d vitellogenin induction NOEC	<0.01	Panter *et al*., 2002	KC: 1 Measured concentrations were ≥56% of nominal.
Onco-rhynchus mykiss (rainbow trout)	4-*tert*-pentylphenol (>99.69% pure)	Hepatoma cells (RTH-149)	Static	N	11	Not stated	Not stated	Not stated	Induction of reporter gene EC_{50}	7.6×10^{-7} M	Hornung *et al*., 2003	KC: 2 Concentrations were not confirmed analytically. Test medium type not stated.
					18					6.9×10^{-7} M		

Note: KC = Klimisch code

4.1.1.2 Acute toxicity to saltwater species

No data are available on the acute toxicity of 4-*tert*-pentylphenol to saltwater fish species.

4.1.1.3 Chronic toxicity in freshwater species

4-*tert*-Pentylphenol belongs to a group of chemicals known as alkylphenols. Higher molecular weight homologues (e.g. 4-*tert*-octylphenol and nonylphenol) have been shown to display oestrogenic properties in various *in vitro* and *in vivo* studies with fish (EC, 2002; EA, 2005b). The oestrogenic and androgenic activities of 4-*tert*-pentylphenol have been investigated in a series of screening studies with mammals, and these are summarised in Section 4.4.9.1. The conclusion is that although the substance appears to have an affinity for the mammalian oestrogen receptor (ER), this finding is irrelevant to the human health risk characterisation since no oestrogenic effects are observed in multigenerational or developmental studies with similar chemicals.

Nevertheless, Henry *et al*. (2001) report that the relative binding affinities (RBA) of alkylphenols to the rainbow trout liver ER are approximately an order of magnitude greater than those reported for the human and rat ERs, indicating greater binding potential of alkylphenols in rainbow trout than in mammals. The rank order RBAs compared to oestradiol was 4-*tert*-octylphenol (RBA = 0.01) > 4-*tert*-pentylphenol (RBA = 0.004) > 4-*tert*-butylphenol (RBA = 0.002). Similar observations are summarised by SFT (2007) for 4-*tert*-butylphenol, and, in some studies, the *in vitro* ER binding affinity of that substance in fish cells appears to be the same as 4-*tert*-octylphenol.

It is therefore possible that the weak oestrogenicity of 4-*tert*-pentylphenol may be more important for fish than mammals. Subtle interference of endocrine system functions can have significant adverse effects on organisms, but standard toxicity tests are not designed to cover such effects (e.g. because they miss windows in the life cycle when the organism is at its most sensitive, or they do not include relevant endpoints). Instead, *in vivo* studies with appropriate endpoints and durations of exposure are needed to establish whether oestrogenicity observed *in vitro* may lead to adverse effects in practice.

Several long-term studies have been performed on fish exposed to 4-*tert*-pentylphenol, most of which focus on endocrine-mediated endpoints. These are described below for each species, except for an OECD study in which several species were studied.

4.1.1.3.1 Medaka (*Oryzias latipes*)

One high quality long-term fish study was found in which medaka (*Oryzias latipes*) were exposed to 4-*tert*-pentylphenol (control, 0.0511, 0.1, 0.224, 0.402 and 0.931 mg/L (measured concentrations)) under flow-through conditions for two generations to investigate effects on survival, growth and reproduction (Seki *et al*., 2003). Breeding pairs were allowed to spawn and 60 eggs (15 per chamber) were then exposed to 4-*tert*-pentylphenol within 12 hours of fertilisation. Five individuals from each test chamber (i.e. 20 per treatment group, except the highest treatment in which only 12 fish survived) were sacrificed 60 days after hatching, and their secondary sexual characteristics recorded, before their bodies were fixed and stained for examination of gonadal histology.

Seventy days after hatching, six mating pairs were selected from each of the three lowest treatment groups (0.0511, 0.1 and 0.224 mg/L) plus the controls, assigned to individual test chambers and exposed for a further period until 101 days after hatching. Eggs spawned from each female were counted and assessed for viability. The mating pairs

were sacrificed at the end of the exposure period, and male secondary sexual characteristics recorded, before measurement of body, gonad and liver weights, and analysis of livers for vitellogenin concentrations.

Eggs spawned from the F_0 females on the last three days of reproduction (99–101 days after hatch) were collected and exposed to 4-*tert*-pentylphenol until they hatched. After hatching, 60 eggs (15 per chamber) were exposed for a further 61 days, in the same way as the parental generation, before sacrifice and measurement of weight, length, secondary sexual characteristics, gonadal histology, and liver vitellogenin concentration.

Measurement of 4-*tert*-pentylphenol concentrations in water sampled from the test chambers was performed every two weeks and remained above 80% of nominal concentrations.

The 60-d survival and growth NOEC in the F_0 generation was 0.402 mg/L. No males were found in the two highest treatment groups, leading to significantly skewed sex ratios and a NOEC for this endpoint of 0.224 mg/L. Induction of testis-ova was significantly higher at 0.224 mg/L, with no incidence of this effect at lower concentrations. Reproduction was also impaired at 0.224 mg/L, with significantly lower mean fertility per mating pair. This reproductive impairment was due to reduced fertility in only two of the six pairs exposed to 0.224 mg/L. Hepatic vitellogenin concentrations in male fish were significantly and similarly elevated at all test concentrations, to levels indistinguishable from those found in female fish.

In the F_1 generation, no effects on mortality were observed at the concentrations tested (0.0511, 0.1 and 0.224 mg/L), but total length was significantly lower at 0.224 mg/L, and the sex ratio was significantly skewed towards females at this concentration. Testis-ova were found at all tested concentrations with an incidence of 1 (5%) at 0.0511 mg/L, 3 (15%) at 0.1 mg/L and 8 (40%) at 0.224 mg/L, with only the last of these differing significantly from controls. However, in the fish with testis-ova in the 0.0511 and 0.1 mg/L treatments, active spermatogenesis could still be observed and the fish displayed external male characteristics.

Taken together these results suggest that demographically important effects, such as reproductive impairment in the F_0 generation, and a significantly skewed sex ratio and effects on growth in the F_1 generation, occur at 0.224 mg/L, with a NOEC at 0.1 mg/L. At this NOEC biological effects such as F_0 vitellogenin induction and F_1 testis-ova still occur but cannot be linked to adverse population consequences because the effects of these endpoints on reproductive function are unclear.

In another study, Hagino *et al*. (2001) exposed newly-hatched medaka (*O. latipes*) larvae for 28 days under flow-through conditions to 0.001, 0.01, 0.1 and 1 mg/L 4-*tert*-pentylphenol plus solvent and undosed controls. Single unreplicated aquaria were used to expose 80 fish larvae per concentration under flow-through conditions. Chemical concentrations were measured on days 0, 14 and 28, but only results from the lowest concentration (0.001 mg/L) are reported in the paper. These were 0.0008, 0.0007 and 0.0007 mg/L on days 0, 14 and 28 respectively. After the 28-d exposure period 30 males and 30 females were selected from each treatment group and placed in separate undosed aquaria. They were then reared for a further two weeks until they reached sexual maturity. Twenty males and 20 females were then sacrificed, fixed in formalin and examined for effects on length or secondary sexual characteristics. The gonads in ten of these males and ten females were also examined in serial cross sections.

No statistical results are presented by Hagino *et al*. (2001) to support their derivation of NOECs for 4-*tert*-pentylphenol. However, graphical results support their identification of a NOEC of 0.01 mg/L 4-*tert*-pentylphenol for effects on the male secondary sexual characteristic ratio *dc/dm* (*dc* = cleft depth between the last ray and preceding one of the dorsal fin; *dm* = maximum length of dorsal fin), and the percentage appearance of small papillary processes on the anal fin. There is also a graphical indication of a decrease in males at 0.1 mg/L in the ratio *am/tl* and *a2/tl* (*am* = maximum length of anal fin; *a2* = length of second ray from the last one of anal fin; *tl* = total length). The authors also identify a LOEC of 0.01 mg/L (i.e. a NOEC of 0.001 mg/L) for differentiation of the gonads of genotypic males into ovaries. However, the supporting graph suggests that at 0.01 mg/L only two sex-reversal male fish were observed out of a sample of ten. This level of incidence is not statistically significant, so the NOEC for this endpoint should be 0.01 mg/L and not 0.001 mg/L. The authors also state that testis-ova were found in 'one or two specimens' exposed to 4-*tert*-pentylphenol at 0.001 and 0.01 mg/L, but do not expand on this statement.

4.1.1.3.2 Common carp (*Cyprinus carpio*)

Gimeno *et al*. (1996, 1997, 1998a,1998b) report the effects of 4-*tert*-pentylphenol on male common carp (*Cyprinus carpio*). Their first study (Gimeno *et al*., 1996) reported on the ability of 4-*tert*-pentylphenol to feminise genotypic male carp. Sexually undifferentiated, 50-day-old fish were exposed for 90 days under intermittent flow-through conditions to 0.1, 0.32 and 1 mg/L 4-*tert*-pentylphenol. Six individuals were sampled every 10 days, starting after 30 days of exposure. The authors state that '…exposure for 60 days to all tested 4-*tert*-pentylphenol concentrations…resulted in the development of an oviduct in almost all male fish.' However, the figure presented in their paper shows that a statistically significant increase in the incidence of oviducts only occurred at 0.32 mg/L, with a NOEC at 0.1 mg/L (albeit one at which there was ~30% incidence of oviducts, but a lack of statistical power meant that this was not significant). A statistically significant reduction in primordial germ cells only occurred at the highest test concentration.

Gimeno *et al*. (1997) in a subsequent paper reported on exposure of males to a fixed concentration of 0.14 mg/L for different periods of time, both before and during sexual differentiation. Brief (3–6 day) exposures of embryos, yolk sac larvae or feeding larvae did not affect sexual differentiation. Exposures lasting four weeks but ending long before the start of sexual differentiation also had no effect on reproductive tract development. In contrast, four-week exposure of fingerlings beginning just before the start of sexual differentiation led to formation of an incomplete oviduct. Even longer exposures, beginning before sexual differentiation, induced the formation of a complete oviduct. It is likely that these fish would have been unable to reproduce because of the absence of a vas deferens. Reduced proliferation of primordial germ cells was also significantly correlated with longer exposures, with no sign of spermatogenesis, and reduction of gonads to an epithelium. Effects on sexual differentiation persisted in individuals returned to undosed water for 59 days. Measured 4-*tert*-pentylphenol concentrations were only about 50% of the nominal concentration, so the NOEC in this study was <0.07 mg/L.

Gimeno *et al*. (1998a, 1998b) report on similar studies with male carp in which fish were exposed to several concentrations of 4-*tert*-pentylphenol. At 50 days post-hatch 120 individuals were placed in each of seven aquaria and exposed under intermittent flow-through conditions to 0.1, 0.32 or 1 mg/L for up to 140 days post-hatch (Gimeno *et al*. 1998a). After 20 days of exposure, six to nine fish were sampled at 10 day intervals for histological examination of the gonads. The plasma of fish remaining at the end of the study was sampled for vitellogenin determination. Water samples were collected and

chemically analysed at regular intervals and were 27–39% of the nominal concentrations (0.036 ± 0.022, 0.09 ± 0.062, and 0.256 ± 0.181 mg/L). After 60 days of exposure all males exposed to 0.09 mg/L, and 33% of fish exposed to 0.036 mg/L had developed an oviduct. After 90 days of exposure, half of the fish exposed to 0.036 mg/L had developed an oviduct and 50% had developed normally into males. However, the number of primordial germ cells was significantly lower than in controls in fish exposed at all concentrations of 4-*tert*-pentylphenol at most sampling times. At the end of the study, plasma vitellogenin levels were significantly higher only at the highest concentration of 0.256 mg/L.

In a further study (Gimeno *et al*., 1998b) sexually mature male carp were exposed for three months in an intermittent flow-through system to nominal concentrations of 0.032, 0.1, 0.32 and 1 mg/L 4-*tert*-pentylphenol. Plasma vitellogenin levels were significantly higher in fish exposed to 1 mg/L for two or three months. After three months of exposure the gonadosomatic index and diameter of the seminiferous lobules were significantly lower at all concentrations when compared to controls, but spermatocrit values were only significantly lower at 1 mg/L. Observation of testes showed that after two months of exposure to the lowest test concentration the testes were less densely filled with spermatozoa, and more severe changes, such as disorganisation of the lobules, atrophy of the germinal epithelium, absence of spermatozoa and necrosis, were observed in three out of five fish exposed to each of the three higher concentrations. These effects were more pronounced after three months of exposure.

4.1.1.3.3 Fathead minnow (*Pimephales promelas*)

Panter *et al*. (2006) reported results from an extended fish early life-stage test with fathead minnow (*Pimephales promelas*) in which embryos (<24-h post-fertilisation) were exposed in a flow-through system to 0.056, 0.18 and 0.56 mg/L 4-*tert*-pentylphenol for up to 107 days post-hatch. Measured concentrations were within 13% of nominal values. Fish were sampled to examine growth and gonadal histology at 30, 60 and 107 days post-hatch. Fish sampled at 107 days post-hatch were also examined for effects on secondary sexual characteristics, gonadosomatic index and plasma vitellogenin. The NOEC for most endpoints at 107 days post-hatch was either 0.18 or 0.56 mg/L, as shown below:

Larval survival NOEC = 0.56 mg/L
Wet weight and standard length NOEC = 0.56 mg/L
Female condition factor NOEC = <0.056 mg/L
Plasma vitellogenin induction NOEC = 0.56 mg/L
Male secondary sexual characteristics NOEC = 0.56 mg/L
Gonadosomatic index NOEC = 0.18 mg/L
Gonadal sex of fish NOEC = 0.18 mg/L
Gonadal attachments NOEC = 0.056 mg/L
Liver and kidney histology NOEC = 0.56 mg/L

The exceptions to this were the presence of gonadal attachments (NOEC = 0.056 mg/L and female condition factor (NOEC <0.056 mg/L). The demographic significance of an increase in gonadal attachments is unclear, as is the significance of a small decline in female condition factor at all tested concentrations of 4-*tert*-pentylphenol when compared with the solvent control. It is likely that a significant reduction in condition factor would not have been found if the comparison had been with the dilution water control, although statistical results for this comparison are not given. Taken together, these results tend to support the results for medaka reported by Seki *et al*. (2003).

4.1.1.3.4 OECD ring test with medaka, fathead minnow and zebrafish

The results from a recent ring test (OECD, 2006) in which several different fish species (medaka, fathead minnow and zebrafish) were exposed to 4-*tert*-pentylphenol also tend to support the results from Seki *et al*. (2003). The ring test report is currently only available as a draft, but data from it have been cited in the open literature (Panter *et al*., 2006). Several different laboratories participated in the study to ring test a standardised fish assay protocol. Reproductively active male and female fish were exposed together for 21 days in two groups of ten (five males and five females in each group) to 0, 0.1, 0.32 and 1 mg/L 4-*tert*-pentylphenol (and other endocrine modulators) before measurement of secondary sexual characteristics, gonadal histology, and vitellogenin levels. One concentration of a positive control was used (17 beta-estradiol). Test concentrations were analysed weekly, and were within 20% of nominal in all but one laboratory. Four laboratories performed tests with medaka, three performed tests with fathead minnow and three performed tests with zebrafish.

For medaka (*Oryzias latipes*) there was no difference in the number of days on which spawning occurred at any test concentration in one laboratory, results were equivocal in a second laboratory and there appeared to be a dose-dependent effect on spawning in the remaining two laboratories. Secondary sexual characteristics (papillary processes on the anal fin) were not significantly affected except at 1 mg/L in one laboratory. Male vitellogenin levels were significantly higher at 0.1 mg/L in three of the four laboratories, and at 0.32 mg/L in all the laboratories. Histology results varied between laboratories, but there was evidence for exposure-related effects on intraluminal histiocytic cells, interstitial fibrosis, nephropathy, and testicular degeneration. These results are consistent with those found for medaka by Seki *et al*. (2003).

For fathead minnow (*Pimephales promelas*) there was a dose-dependent reduction in spawning in all three laboratories, with no spawning at 1 mg/L; however, spawning in the control vessels was very low due to crowding. Secondary sexual characteristics (nuptial tubercles) were significantly reduced in males exposed to 1 mg/L in all three laboratories, and at 0.32 mg/L in one laboratory. Male vitellogenin levels were significantly higher at 0.32 mg/L in the two laboratories that were able to report results. Histology results varied between laboratories, but there was evidence for exposure-related effects on increased spermatagonia, proteinaceous fluid and testicular degeneration.

For zebrafish (*Danio rerio*) there was no apparent difference in spawning at any concentration in any of the three laboratories, but mean fertilisation rate and total number of eggs per day were reduced in one laboratory at 1 mg/L which conducted such investigations. Zebrafish do not have measurable secondary sexual characteristics, so these endpoints could not be assessed in this study. Male vitellogenin levels were significantly higher at 0.1 mg/L in one of the three laboratories, at 0.32 mg/L in two of the laboratories, and at 1 mg/L in all three laboratories. Histology results varied between laboratories, but there was evidence for exposure-related effects on increased spermatagonia.

It is possible that additional studies may be performed under this programme in the future.

4.1.1.4 Summary of chronic effects in freshwater fish

The most reliable multigenerational NOEC for fish is 0.1 mg/L, obtained in the study on medaka reported by Seki *et al*. (2003). This study had the longest duration and was the

best performed of those available. The medaka study by Hagino *et al*. (2001) appears to have been performed reasonably well, but there was a lack of true replication and an absence of statistical analyses. This NOEC is also supported by data from the recent OECD ring test (OECD, 2006) and Panter *et al*. (2006).

The results for common carp reported by Gimeno and co-workers are of concern, but do not provide sufficient information to derive a PNEC because effects were observed at the lowest concentrations in all the studies except the first (Gimeno *et al*. 1996). In addition, measured test concentrations as a percentage of nominals were much lower than would normally be acceptable under standard guidelines and exposures were not replicated. However, the results do indicate the possibility that effects on gonadosomatic index and reproductive tract development may occur at concentrations below the medaka NOEC. Therefore, although the medaka multigenerational NOEC of 0.1 mg/L is preferred in this risk evaluation to represent chronic toxicity for fish, the Gimeno *et al*. (1997, 1998a, 1998b) results will be considered when applying an assessment factor in Section 4.1.6.1.

4.1.2 Toxicity to aquatic invertebrates

Toxicity data for freshwater and saltwater invertebrate species exposed to 4-*tert*-pentylphenol were reviewed and are summarised in Table 4.3.

4.1.2.1 Acute toxicity in freshwater species

Acute LC_{50} values for freshwater crustaceans were between 1.8 and 2.7 mg/L (with NOECs between 1.0 and 1.6 mg/L).

4.1.2.2 Acute toxicity in saltwater species

Acute LC_{50} values for saltwater crustaceans were between 1.7 and 6.5 mg/L (with a NOEC of 1.0 mg/L).

4.1.2.3 Chronic toxicity in freshwater species

No true chronic data were found for freshwater invertebrates. However, Wang *et al*. (2005) report a study in which gravid female *Daphnia magna* were exposed to several different chemicals, including 4-*tert*-pentylphenol, until they produced their third brood. The individuals in each brood were then examined to establish the presence of males in order to determine any interference with normal juvenoid hormonal activity. No males were found at the single concentration of 1.0 mg/L used in this study, and there was no evidence from additional studies that 4-*tert*-pentylphenol possessed any anti-juvenoid activity.

4.1.2.4 Chronic toxicity in saltwater species

No chronic toxicity data are available for saltwater invertebrate species exposed to 4-*tert*-pentylphenol.

4.1.3 Toxicity to aquatic primary producers

4.1.3.1 Freshwater species

One freshwater algal study was found in which *Pseudokirchneriella subcapitata* was exposed to 4-*tert*-pentylphenol for 96 hours, and inhibition of the average specific growth rate was determined (Davoren & Fogarty, 2005). The results are summarised in Table 4.4. The 96-h EC_{50} and NOEC from this study were 4.2 and 3.2 mg/L respectively.

4.1.3.2 Saltwater species

No toxicity data are available for saltwater primary producers exposed to 4-*tert*-pentylphenol.

Table 4.3 Toxicity of 4-*tert*-pentylphenol to freshwater and saltwater invertebrates

Species	Chemical tested	Age/ size	Static/ flow-through	Test conc. meas. ?	Temp. (°C)	Dissolved oxygen (mg/L)	Hardness (mg $CaCO_3$/L) or salinity (‰)	pH	Endpoint & concentration (mg/L)		Ref.	Validity & comments
Freshwater												
Daphnia magna (water flea)	4-*tert*-pentylphenol (99% pure)	Juvenile < 24h old	Semi-static	Y	20	> 60% saturation	227	7.8–8.4	96-h NOEC (survival)	1.8	Gerritsen *et al*., 1998	KC: 1
	4-*tert*-pentylphenol sodium salt (purity not stated)	Juvenile < 24h old	Static	N	20	Not stated (but continuous aeration provided)	Not stated	Not stated	48-h immobilisation EC_{50}	2.7	Davoren & Fogarty, 2005	KC: 2 Test concentrations were not confirmed analytically.
									48-h immobilisation NOEC	1.6		
	tert-amylphenol (purity not stated)	Gravid female (7–14 d old)	Semi-static	N	20	Not stated	192	Not stated	Stimulation of male offspring production and anti-juvenoid activity NOEC	>1.0	Wang *et al*., 2005	KC: 2 Limit test.
Thamnocephalus platyurus (fairy shrimp)	4-*tert*-pentylphenol sodium salt (purity not stated)	Hatched cysts	Static	N	25	Not stated	Not stated	Not stated	24-h LC_{50}	2.1	Davoren & Fogarty, 2005	KC: 2 Test concentrations were not confirmed analytically.
									NOEC	1.0		
Saltwater												
Crangon septemspinosa (shrimp)	p-*tert*-pentylphenol (purity not stated)	Weight: 2 g	Static	Y	10	Not stated	Not stated	-	96-h LC_{50}	1.7	McLeese *et al*., 1981	KC: 2 No replication (only four shrimps per concentration). Test medium type not stated.
Artemia salina (brine shrimp)	4-*tert*-pentylphenol sodium salt (purity not stated)	Hatched cysts	Static	N	25	Not stated	Not stated	-	24-h LC_{50}	6.5	Davoren & Fogarty, 2005	KC: 2 Test concentrations were not confirmed analytically.
									NOEC	1.0		

Note: KC = Klimisch code

Table 4.4 Toxicity of 4-*tert*-pentylphenol to freshwater algae and micro-organisms

Species	Chemical tested	Age/ size	Static/ flow-through	Test conc. meas. ?	Temp. (°C)	Dissolved oxygen (mg/L)	Hardness (mg $CaCO_3$/L) or salinity (‰)	pH	Endpoint & concentration (mg/L)		Ref.	Validity & comments
Pseudokirchneriella subcapitata (green alga)	4-*tert*-pentylphenol sodium salt (purity not stated)	Exponential growth	Static	N	25	No	Not stated (prepared in APHA (1995) medium)	Not stated	96-h EC_{50}	4.2	Davoren & Fogarty, 2005	KC: 2 Test concentrations were not confirmed analytically.
									NOEC	3.2		
Tetrahymena thermophilia (ciliated protozoan)	4-*tert*-pentylphenol sodium salt (purity not stated)	Protozoan culture	Static	N	30	Not stated	Not stated	Not stated	24-h EC_{50}	4.5	Davoren & Fogarty, 2005	KC: 2 Test concentrations were not confirmed analytically.
									NOEC	1.8		
Tetrahymena pyriformis (ciliated protozoan)	4-*tert*-pentylphenol (purity not stated)	Axenic culture	Static	N	Not stated	Not stated	Not stated	Not stated	48-h EC_{50}	9.6	Schultz, 1987	KC: 2 Test concentrations were not confirmed analytically.
Vibrio fischeri	4-*tert*-pentylphenol sodium salt (purity not stated)	Freeze-dried cells	Static	N	25	No	Not stated	Not stated	15 min EC_{50}	0.03	Davoren & Fogarty, 2005	KC: 2 Test concentrations were not confirmed analytically.

Note: KC = Klimisch code

4.1.4 Toxicity to micro-organisms

Studies on micro-organisms were reviewed and are summarised in Table 4.4.

Two studies were found in which ciliated protozoans were exposed to 4-*tert*-pentylphenol. Davoren & Fogarty (2005) report a 24-h EC_{50} of 4.5 mg/L and a NOEC of 1.8 mg/L for *Tetrahymena thermophilia*. Schultz (1987) reports a 48-h EC_{50} of 9.6 mg/L for *Tetrahymena pyriformis.*

A bacterial test was also reviewed in which *Vibrio fischeri* was exposed to 4-*tert*-pentylphenol for 15 minutes and inhibition of bioluminescence was measured (Davoren & Fogarty, 2005). The EC_{50} from this study was 0.03 mg/L. However, *V. fischeri* is a saltwater organism, so is not a relevant species for assessing effects in sewage treatment plants.

4.1.5 Toxicity to other types of organism

No data were found on the toxicity of 4-*tert*-pentylphenol to amphibians or sediment-dwelling organisms.

4.1.6 Predicted no-effect concentrations for the aquatic compartment

4.1.6.1 Calculation of a PNEC for surface water

Fish, *Daphnia* and algae represent different trophic levels in an aquatic food chain. In acute tests, all three groups appear to have a comparable sensitivity to 4-*tert*-pentylphenol. Reliable and relevant long-term NOECs are also available for fish and algae, but not for invertebrates. The preferred NOEC for fish is 0.1 mg/L from the Seki *et al*. (2003) study on medaka, based on reproductive impairment and skewed sex ratio. The NOEC for algae is 3.2 mg/L for *Pseudokirchneriella subcapitata* (Davoren & Fogarty, 2005). When two long-term NOECs are available for two trophic levels, the TGD recommends application of an assessment factor of 50 to the lower of the two. This results in a $PNEC_{freshwater}$ of 0.002 mg/L (2 µg/L).

There are two main elements of uncertainty that affect the size of the assessment factor in this case, as follows:

- *Are fish the most sensitive trophic level on which to base the PNEC?*
  Although there is no significant difference in sensitivity of the three trophic levels in acute tests, 4-*tert*-pentylphenol is a weak oestrogen (Section 4.1.1.3) and so fish might be expected to be of higher chronic sensitivity than invertebrates or algae. However, the lack of chronic toxicity data for *Daphnia* means there is some uncertainty about this. Data are available for the close analogue 4-*tert*-butylphenol (SFT, 2007), and a comparison of toxicity data is provided in Table 4.5. For consistency, the comparison has been made using data for the same species, although interspecies differences for acute endpoints are low. The use of NOEC data is a slight complication, since the value depends on the dosing used in the experiment.

Table 4.5 Comparison of aquatic toxicity data between 4-*tert*-butylphenol and 4-*tert*-pentylphenol

Species	Endpoint	Unit	4-*tert*-butylphenol	4-*tert*-pentylphenol
-	Molecular weight	g/mol	150.22	164.25
-	Log K_{ow}	-	3.3	4.0
Oryzias latipes	96-h LC_{50}	mg//L	5.1	2.6
		µmol/L	34	16
	Chronic NOEC	mg//L	-	0.1
		µmol/L	-	0.6
	Acute/chronic ratio		-	26
Daphnia magna	48-h EC_{50}	mg//L	5.0[a]	2.7
		µmol/L	33	16
	21-d NOEC	mg//L	0.73	-
		µmol/L	4.8	-
	Acute/chronic ratio		6.8	-
Pseudo-kirchneriella subcapitata	96-h E_rC_{50}	mg//L	14[b]	4.2
		µmol/L	93	26
	96-h NOEC	mg//L	0.32	3.2
		µmol/L	2.1	19
	Acute/chronic ratio		44	1.3

Note: a – This is the geometric mean of the three values available.
b – Two valid algal studies are available for 4-*tert*-butylphenol, but the NOECs are quite different. The second study only measured biomass, but the 96-h EC_{50} and NOEC were 23 and 9.5 mg/L respectively, giving an acute–chronic ratio of 2.4.

4-*tert*-Pentylphenol is more acutely toxic to aquatic organisms than 4-*tert*-butylphenol (by a factor of ~2), as would be expected from its higher hydrophobicity.

Considering higher molecular weight alkylphenols, no *Daphnia* data are available for hexyl- or heptylphenol (see Appendix 1), but relevant acute and chronic data are available for both 4-*tert*-octylphenol and nonylphenol (this last substance has a complex mixture of alkyl chain lengths, unlike the others) (EA, 2005b; EC, 2002). These two analogues are more hydrophobic than 4-*tert*-pentylphenol, and are an order of magnitude more toxic in acute tests. The *Daphnia* acute–chronic ratios are in the range 4.4–9 for 4-*tert*-octylphenol and 3.5 for nonylphenol, and *Daphnia* are an order of magnitude less sensitive than fish in chronic studies with both substances.

In summary, none of these analogue substances has an acute–chronic ratio for *Daphnia* above 10. This implies that the 21-d *Daphnia* NOEC for

4-*tert*-pentylphenol would be around 0.3 mg/L as a worst case, which is higher than the fish NOEC. It is therefore unlikely that *Daphnia* would be significantly more sensitive to 4-*tert*-pentylphenol than fish over long-term exposures. In such cases it is usually justified to apply an assessment factor of 10 to the lowest NOEC, and so the $PNEC_{freshwater}$ would become 10 µg/L. However, EA (2005b) notes that other aquatic invertebrates – notably snails and the shrimp *Gammarus* – could be more sensitive than fish for 4-*tert*-octylphenol.

- *Are other fish species more sensitive than medaka?* During independent peer review of this report, expert judgement was divided over which long-term fish NOEC endpoint is the most robust and relevant for derivation of the $PNEC_{freshwater}$. The results reported by Seki *et al*. (2003) for medaka are considered to be the most reliable. However, other – generally less reliable – studies have reported effects at concentrations below 0.1 mg/L, not only for medaka but also common carp and fathead minnow (see Section 4.1.1.3). While some of the effects might not have any significance at the population level, the observed effects on carp (e.g. feminisation of male gonads) are worrying, especially given that a NOEC has not been established.

  A $PNEC_{freshwater}$ of 2 µg/L would provide a margin of safety of 5 when compared to the most reliable NOEC reported by Hagino *et al*. (2001) and a margin of safety of 16 when compared to the unbounded LOEC for carp of 0.032 mg/L reported by Gimeno *et al*. (1998b). It is therefore not considered justified to use a lower assessment factor than 50 based on the available evidence. If an assessment factor of 50 were applied to the unbounded LOEC for carp, the $PNEC_{freshwater}$ would be ~0.6 µg/L.

  No chronic fish studies are available for 4-*tert*-butylphenol for comparison (SFT, 2007), although an extended early life stage test is currently under way. A preliminary range-finding study suggests that there might be effects on females (e.g. condition) with possible consequences for egg hatchability.

The weight of evidence therefore suggests a $PNEC_{freshwater}$ somewhere in the range 0.6–10 µg/L. The equivalent PNECs for 4-*tert*-butylphenol and 4-*tert*-octylphenol are 6.4 and ~0.1 µg/L respectively (EA, 2005b; SFT, 2007), both derived using an assessment factor of 50. **A $PNEC_{freshwater}$ of 2 µg/L** will therefore be used in the risk characterisation as a reasonably conservative and consistent value, but the effect of using a different PNEC will also be discussed.

No long-term saltwater data are available for 4-*tert*-pentylphenol. Under these circumstances the TGD recommends application of an assessment factor of 500 to the lower of two long-term NOECs from freshwater species. This, in effect, adds a further assessment factor of 10 to the $PNEC_{freshwater}$ derived for the freshwater environment. The **$PNEC_{saltwater}$ is therefore 0.2 µg/L**.

4.1.6.2 Calculation of PNEC for sediment

No sediment toxicity data are available, so the $PNEC_{freshwater\ sediment}$ must be estimated within EUSES by using equilibrium partitioning assumptions and the $PNEC_{freshwater}$. This results in a **$PNEC_{freshwater\ sediment}$ of 0.105 mg/kg wet weight**.

A **$PNEC_{marine\ sediment}$ of 0.010 mg/kg wet weight** is derived from the $PNEC_{saltwater}$ in the same way.

4.1.6.3 Calculation of PNEC for WWTP micro-organisms

The TGD recommends that for ciliated protozoa, assessment factors of 10 or 1 should be applied to EC_{50} or NOEC data respectively, to calculate a $PNEC_{WWTP}$. The most sensitive value for protozoa is a 24-h NOEC of 1.8 mg/L for *Tetrahymena thermophilia* reported by Davoren & Fogarty (2005). This results in a **$PNEC_{WWTP}$ of 1.8 mg/L**.

4.2 Terrestrial compartment

4.2.1 Terrestrial toxicity data

No terrestrial toxicity data were found for 4-*tert*-pentylphenol.

4.2.2 Calculation of PNEC for the soil compartment

No soil toxicity data are available, so a screening $PNEC_{soil}$ must be estimated using equilibrium partitioning assumptions and the $PNEC_{freshwater}$. This results in a **$PNEC_{soil}$ of 0.084 mg/kg wet weight**. The possible range of values for the $PNEC_{freshwater}$ has consequences for the screening $PNEC_{soil}$, and so this will also be considered in the risk characterisation.

4.3 Atmospheric compartment

No relevant data are available. Based on its structure, the substance is not considered to possess Global Warming Potential (GWP), Ozone Depletion Potential (ODP) or Photochemical Ozone Creation Potential (POCP) properties.

4.4 Mammalian toxicity data

Data are available for 4-*tert*-pentylphenol for the endpoints of acute oral toxicity, skin irritation, eye irritation, skin sensitisation, repeated dose dermal toxicity, mutagenicity and developmental toxicity. Since a number of toxicology endpoints have not been adequately investigated, this assessment will of necessity involve predictions based on toxicokinetic and toxicity data for structurally related alkylphenols, in particular 4-*tert*-butylphenol (SFT, 2007). Justification for the read-across approach for the endpoints of toxicokinetics, repeat dose toxicity and reproductive toxicity is presented in Appendix 3.

4.4.1 Toxicokinetics

4.4.1.1 Studies in animals

No toxicokinetic data are available for 4-*tert*-pentylphenol. However, since the toxicokinetics of 4-*tert*-butylphenol, 4-*tert*-octylphenol and nonylphenol have been studied in the rat, these data will be used to predict the toxicokinetic behaviour of 4-*tert*-pentylphenol.

In the first of three 4-*tert*-butylphenol studies, radiolabelled test material (147 µg/kg/d) was given to three male Wistar rats by oral gavage on 3 successive days (Freitag *et al*., 1982). Mass balance measurements showed that 26.7 and 72.9% of the administered radioactivity was excreted in the faeces and urine respectively. The proportion of the administered radioactivity remaining in the body 7 days after dosing was negligible (0.1%).

In the second 4-*tert*-butylphenol study, male Wistar rats (four animals/dose) were given a single intravenous dose of 1.2–10.3 mg/kg radiolabelled test material (Koster *et al*., 1981). Between 91 and 93% of the radioactivity was recovered from the urine and bile within 4 hours of dosing. No information regarding the relative proportions of radioactivity in the urine and bile was provided, but the proportions of the applied radioactivity excreted as the glucuronide and sulphate conjugates were 65–71% and 17–21% respectively. In addition, *in vitro* studies with isolated rat hepatocytes showed that at all concentrations of 4-*tert*-butylphenol tested (25–800 µM) the main metabolite was the glucuronide, with the sulphate being produced in smaller amounts.

The third 4-*tert*-butylphenol study investigated the excretion of the sulphate conjugate in the rat (Nanbo, 1991). A single dose of radiolabelled test material (18 mg/kg) was given intravenously to animals, and bile and urine collected for 24 hours after dosing. The sulphate conjugate was detected in the urine but not in the bile.

The toxicokinetics studies with nonylphenol and 4-*tert*-octylphenol have been described in more detail in an unpublished addendum to EA (2005b).

The studies with 4-*tert*-octylphenol showed that after oral dosing to rats this alkylphenol was rapidly absorbed from the gastrointestinal tract (Hüls, 1995a, 1995b, 1996a, 1996b; Certa *et al*., 1996). The extent of absorption was not addressed in these studies; the bioavailability of 4-*tert*-octylphenol was found to be low (2–10%), but it was unclear how much this reflected poor absorption from the gut and how much it reflected efficient first-pass metabolism. After oral dosing, 4-*tert*-octylphenol was found in the liver, adipose tissue, kidney and muscle. As the dose of 4-*tert*-octylphenol increased, the proportion in the adipose tissue also tended to increase, but from the available data it was unclear whether significant bioaccumulation of 4-*tert*-octylphenol occurs on repeated dosing.

The most comprehensive study with nonylphenol found that a significant proportion (>50 %) of the administered dose was absorbed from the gastrointestinal tract after oral dosing; unconjugated nonylphenol present in the faeces was likely to represent unabsorbed material (Green *et al*., 2003). After absorption, nonylphenol was metabolised to the glucuronide and excreted, mostly in the bile. There was evidence from female rats that the hepatic metabolism of nonylphenol is subject to saturation at high doses. Other studies showed that absorbed nonylphenol distributes to the liver, kidney, skeletal muscle and brain, and confirmed that glucuronidation is the main metabolic pathway for nonylphenol in rat liver (Doerge *et al*., 2002; Daidoji *et al*., 2003). A study with a straight-chain nonylphenol (4-*n*-nonylphenol) found evidence for significant oxidation of the alkyl chain (Zalko *et al*., 2003).

4.4.1.2 Studies in humans

No human data are available for 4-*tert*-pentylphenol, but a limited study with nonylphenol found that the oral bioavailability of the parent compound was approximately 20% (Müller, 1997). About 10% of the oral dose was excreted in urine as parent compound or conjugated nonylphenol, mostly within 8 hours of dosing.

4.4.1.3 Summary of toxicokinetics

No toxicokinetic data are available for 4-*tert*-pentylphenol. On the basis of studies conducted with nonylphenol, 4-*tert*-octylphenol and 4-*tert*-butylphenol in the rat, it is predicted that a significant proportion of 4-*tert*-pentylphenol (>50 %) will be absorbed after oral dosing, with the remainder being voided unchanged in the faeces. After absorption it is expected that 4-*tert*-pentylphenol will be distributed to the liver, kidney, skeletal muscle and brain, but distribution to the male and female reproductive organs is likely to be limited. It is expected that 4-*tert*-pentylphenol will be subject to first-pass metabolism in the liver to glucuronide and sulphate conjugates. From a study with 4-*tert*-butylphenol it is predicted that these metabolites will be excreted extensively in the urine, and to a lesser extent in the bile. It is predicted that the toxicokinetics of 4-*tert*-pentylphenol will be similar for different mammalian species.

4.4.2 Acute toxicity

4.4.2.1 Studies in animals

4.4.2.1.1 Inhalation

No acute inhalation toxicity data are available for 4-*tert*-pentylphenol. However, an acute inhalation toxicity study conducted in the rat with an aerosol of 4-*tert*-butylphenol derived a 4-h LC_{50} of >5,600 mg m^{-3} (Klonne *et al*., 1988). It is predicted that 4-*tert*-pentylphenol will also be of low acute toxicity by the inhalation route.

4.4.2.1.2 Oral

Acute oral toxicity tests have been conducted with 4-*tert*-pentylphenol in the rat (IHFCAY, 1967; Hüls, 1995c). In the more recent study, conducted to OECD guidelines, five male and five female animals were given 4-*tert*-pentylphenol in corn oil by gavage at a limit dose of 2,000 mg/kg. There were no deaths, but clinical signs of toxicity included abnormal movements, sedation and diarrhoea. At necropsy 1/5 males and 1/5 females

were found to have adhesions between the gastrointestinal tract and other internal organs. In the older study, for which no experimental details are available, an LD_{50} of 1,830 mg/kg was reported. Because of the limited reporting of the older study in the secondary literature source available, the more recent guideline study is considered more relevant for classification.

4.4.2.1.3 Dermal

No acute dermal toxicity data are available for 4-*tert*-pentylphenol, but data are available for 4-*tert*-butylphenol from a study in rabbits (Klonne *et al*., 1988). The test material was applied to five male and five female New Zealand rabbits at doses of 2,000, 8,000, and 16,000 mg/kg for 24 hours. Toxicity was evident at the middle and high dose groups as decreased body weight gain and severe skin irritation. In one female rabbit prostration was observed at 16,000 mg/kg body weight. No lethality was observed in this study, and it was concluded that the LD_{50} was >2,000 mg/kg.

4.4.2.2 Studies in humans

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.2.3 Summary of acute toxicity

By the oral dosing route, the acute toxicity of 4-*tert*-pentylphenol is low. On the basis of studies conducted with 4-*tert*-butylphenol, it is predicted that the acute toxicity of 4-*tert*-pentylphenol by the inhalation and dermal routes of exposure is also low.

4.4.3 Irritation

4.4.3.1 Studies in animals

4.4.3.1.1 Skin

The potential of 4-*tert*-pentylphenol to cause skin irritation has been studied in a standard *in vivo* test in the rabbit conducted to OECD guideline 404 and GLP (Hüls, 1988). Severe oedema and erythema (grade 4), which persisted during standard scoring times, were reported. Necrosis of the treated area was observed after exposure for 1 hour, but not after 3 minutes' exposure. Two days after treatment a hardening crust was seen and at study termination on day 6 a soft crust was seen. In another *in vivo* GLP-compliant guideline study similar corrosive effects were seen after dermal exposure of rabbits to 4-*tert*-pentylphenol for 4 hours; administration for 3 minutes caused very slight, reversible erythema (Safepharm, 1991).

4.4.3.1.2 Eye

In two eye irritation tests conducted in the rabbit by the Draize methodology, 4-*tert*-pentylphenol was found to cause severe eye irritation (Union Carbide, 1964; IHFCAY, 1967).

4.4.3.1.3 Respiratory tract

Although not directly studied, on the basis of the results of the skin irritation studies it can be anticipated that 4-*tert*-pentylphenol has the potential to cause respiratory tract irritation. There is some information on the potential of 4-*tert*-butylphenol to cause irritation of the respiratory tract from the acute inhalation toxicity study of Klonne *et al*. (1988). In that study rats exposed for 4 hours to an aerosol at a limit dose of 5,600 mg/m^3 showed signs of mucosal irritation (perinasal, perioral, and periocular encrustation) and signs of respiratory distress (audible respiration, gasping, and a decreased respiration rate).

4.4.3.2 Studies in humans

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.3.3 Summary of irritation

The above studies show that 4-*tert*-pentylphenol can cause severe irritation to the skin and eyes and at very high exposures might also cause irritation to the respiratory tract.

4.4.4 Corrosivity

The skin irritation tests described in Section 4.4.3 show that 4-*tert*-pentylphenol is corrosive.

4.4.5 Sensitisation

4.4.5.1 Studies in animals

In a standard Bühler test, 4-*tert*-pentylphenol gave positive results (Hüls, 1996c). The material caused sensitisation in 10 out of 20 animals, compared with 0 out of 10 negative control animals.

4.4.5.2 Studies in humans

4.4.5.2.1 Skin

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.5.2.2 Respiratory tract

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.5.3 Summary of sensitisation

On the basis of the positive result in the Bühler test, it is concluded that 4-*tert*-pentylphenol is a skin sensitiser. No information on the potential for respiratory tract sensitisation is available.

4.4.6 Repeated dose toxicity

4.4.6.1 Studies in animals

4.4.6.1.1 Inhalation

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.6.1.2 Oral

There are no data from standard oral repeated dose toxicity studies with 4-*tert*-pentylphenol, but limited information from a standard prenatal developmental toxicity study is available (Siglin, 1991). In this study 4-*tert*-pentylphenol was administered by oral gavage to pregnant Sprague-Dawley rats (25 per dose) from gestation day 6 to 15. Doses were 0, 50, 200 and 500 mg/kg/d and dams and litters were sacrificed and examined after termination of the study on gestation day 20. There was evidence of significant maternal toxicity at the top two doses; the incidence of hair loss, abnormal respiratory sounds and mucoid/soft stools were increased and body weight gain and food consumption were decreased by 10–50%. The NOAEL for repeat dose toxicity for this study was 50 mg/kg/d.

Although the oral repeated dose toxicity of 4-*tert*-pentylphenol has been investigated only to a limited extent, the effects of repeated exposure to 4-*tert*-butylphenol has been investigated in four toxicology studies using oral dosing schedules.

The first study is a recent multigenerational study conducted according to OECD guideline 416 and in compliance with GLP (Clubb & Jardine, 2006). Groups of Sprague-Dawley rats (24–28 per sex, dose and generation) were fed 4-*tert*-butylphenol in the diet at concentrations of 0, 800, 2,500 or 7,500 ppm, corresponding to dose levels of approximately 70, 200 or 600 mg/kg/d. Among non-reproductive organs, macroscopic examination of the eyes, kidney, liver, lung, lymph nodes, skin, stomach, thymus, bone and heart was carried out in F_0 and F_1 adults. In both F_0 and F_1 generations the histopathology of the adrenal and pituitary glands of all control and high dose animals were examined, and the lymph glands, thymus, kidney and skin of a small number of control and high dose animals of the F_0 generation were also studied.

In all generations and in both sexes, body weight gain at 7,500 ppm was 20–32% lower than in controls, and food consumption was 10–25% lower than in controls. At 2,500 ppm body weight gain in the F_0 generation was lower than in controls (17% lower in females and 8% lower in males). In the F_1 generation body weight was transiently lower in males at 800 ppm (weeks 3–5) and 2,500 ppm (weeks 3–9) and in females at 2,500 ppm (weeks 4–5), but average body weight gains over the whole study period were not affected. There were no consistent effects on body weights and food consumption at 800 ppm. The only consistent differences in the weights of non-reproductive organs were low adrenal gland weights in high dose females (absolute weight 20–30% lower than in controls, relative weight 16–22% lower). The only histological changes were seen in the kidney; this organ was subject to a limited examination in control and high dose male animals of the F_0 generation, and no animals of the F_1 or F_2 generations were studied. Of the six high dose F_0 males animals studied, four had chronic progressive nephropathy, two had localised glomerulonephritis, one had focal hyperplasia of the transitional epithelium, one had hydronephrosis and one had localised cystic tubules. These conditions were not observed in either of the two control F_0 males studied.

In summary, this study found evidence of treatment-related effects on body weight gain at 2,500 and 7,500 ppm. In addition, histological abnormalities were described in the kidneys of high dose male animals; low and middle dose animals were not investigated. It should be noted that this study does not provide a complete investigation of the general toxicity of 4-*tert*-butylphenol. In particular because of the limited nature of the renal histology investigations there is uncertainty over whether these changes can be attributed to treatment, and whether kidney changes occur at the bottom two doses. However, some reassurance of the absence of kidney toxicity at the lower doses is provided by the results of the screening study (Japanese Ministry of Health and Welfare, 1996) summarised below. Thus, it is concluded that a NOAEL of 800 ppm, corresponding to 70 mg/kg/d for repeat dose toxicity can be identified from this study.

The second study is a combined repeated dose/reproductive toxicity screening study conducted according to OECD guideline 422 and in compliance with GLP (Japanese Ministry of Health and Welfare, 1996). In a range-finding investigation, the test material was given by oral gavage to male and female Sprague-Dawley rats (5 per dose and sex) at doses of 0, 250, 500 or 1,000 mg/kg/d for 14 days. In this range-finding investigation, 3/5 females and 1/5 males treated at 1,000 mg/kg/d died, with deaths occurring before day 9 and being ascribed to respiratory difficulty. At 250 and 500 mg/kg/d 1/10 and 6/10 animals had abnormal respiratory sounds.

In the full study, 8-week old male and female rats (13 per dose and sex) were administered 4-*tert*-butylphenol by oral gavage at 0, 20, 60 or 200 mg/kg/d. Males were dosed for 28 days, whereas the females were dosed from 14 days prior to mating until day 4 after giving birth (approximately 39 days in all). Clinical signs, food consumption, body weights, organ weights, haematology, serum biochemistry, gross necropsy, and the histopathology of several organs (including the liver, kidney, thymus, spleen, lung, bladder and forestomach, glandular stomach and reproductive organs) were all studied. In this full study some females at 200 mg/kg/d had abnormal respiratory sounds. This is likely to have been caused by local irritation of the respiratory tract during gavage dosing. Treatment with 4-*tert*-butylphenol had no effects on body weight or food consumption, and the only effect on organ weight was a slight (<5 %) increase in mean relative liver weight in males at the top dose. The plasma concentration of albumin in the males was decreased at 60 and 200 mg/kg/d (by 6 and 13% respectively), while in males at 200 mg/kg/d plasma protein was decreased by 6%, red blood cell count was decreased by 5% and white blood cell count was increased by 38%. There were no effects on gross morphology or histology at any dose.

In summary, this study found no convincing evidence of systemic toxicity, including effects on the kidney, after oral dosing at 200 mg/kg/d for 28 days (males) and 39 days (females). The abnormal respiratory sounds and increases in white cell count reported at 200 mg/kg/d are likely to be secondary to local irritation of the respiratory tract during gavage dosing. The NOAEL for this study is considered to be 60 mg/kg/d, based on laboured breathing in females at 200 mg/kg/d.

In the third study 4-*tert*-butylphenol (0 or 15,000 ppm: approximately 600 mg/kg/d) was administered to male Fischer 344 rats (15 per group) in the diet for 51 weeks (Hirose *et al*., 1988). In this non-guideline study only limited investigations were conducted; these included measurements of weight of the whole body, liver and kidneys and assessment of the histology of the glandular stomach, forestomach, oesophagus and intestines. Treatment with 4-*tert*-butylphenol was found to cause body weight and relative liver weight to decrease by 16 and 9% respectively, and relative kidney weight to increase by 82%. The only histological effects of treatment were increases in the incidence of hyperplasia (93% compared with 0% in controls) and papilloma (7% compared with 0% in controls) in the forestomach epithelium.

In another non-guideline study 4-*tert*-butylphenol (0 or 15,000 ppm: approximately 1,230 mg/kg/d) was administered to male Syrian golden hamsters (15 per group) in the diet for 20 weeks (Hirose *et al*., 1986). In this study investigations were limited to measurement of weight of the whole body, liver and kidneys, and assessment of the histology of the urinary bladder, forestomach and glandular stomach. In these tissues the extent of cell proliferation was also investigated by measurement of radiolabelled thymidine uptake by autoradiography. In this study, treatment with 4-*tert*-butylphenol caused a 5% decrease in body weight and a 21% increase in relative liver weight. There were no effects on histology or cell proliferation of the glandular stomach or urinary bladder. However in the forestomach epithelium mild, moderate and severe hyperplasia was more prevalent in treated animals (incidences 100, 80 and 73% respectively) than in controls (incidences 47, 7 and 0% respectively), and the incidence of papillomatous lesions was higher (47%) than in controls (0%). Cell proliferation, measured by thymidine uptake, was also significantly higher in the forestomach of treated animals (274% of control value).

In summary, these two non-guideline studies demonstrate that in rodents oral administration of 4-*tert*-butylphenol can cause proliferation of the forestomach epithelium, probably secondary to chronic irritation.

4.4.6.1.3 Dermal

In a 90-day dermal toxicity study, 4-*tert*-pentylphenol was applied to the skin of Sprague-Dawley rats (10 males and females per dose) at doses of 0, 2.5, 10 and 25 mg/kg/d for 6 hours/day, 5 days/week (Troxel, 1998 (secondary report of a study performed in 1964)). It is unclear from the information available for this study whether the study design was consistent with internationally recognised guidelines. There were no treatment-related deaths, clinical signs, or changes in haematological or clinical chemistry parameters or body weight. However, at 10 and 25 mg/kg/d there was dose-dependent irritation of the treated skin, shown by erythema, desquamation and eschar formation. The eschar developed to cover 10–25% of the application site in 4/20 animals at 10 mg/kg/d, and 50–75% of the application site in 8/20 animals at 25 mg/kg/d. In addition, ulceration was observed in 6/20 animals at 25 mg/kg/d. Histological changes were limited to the treated skin; minimal to marked acanthosis, minimal to mild dermatitis, and inflammatory exudate and ulcers were seen at the top two doses. In summary, in this study there was no evidence of systemic toxicity even at the top dose of 25 mg/kg/d, but the NOAEL for local effects was 2.5 mg/kg/d, based on irritation.

4.4.6.2 Studies in humans

The occupational health literature includes several reports of vitiligo, a depigmentation of the skin, in workers occupationally exposed to 4-*tert*-pentylphenol (Stevenson, 1984). The pathogenesis of vitiligo involves effects on melanocytes but is poorly understood. The interpretation of these studies is complicated by the facts that the workers had also been exposed to other chemicals and the association between vitiligo and 4-*tert*-pentylphenol does not appear to have been studied systematically.

4.4.6.3 Summary of repeated dose toxicity

The developmental study conducted with 4-*tert*-pentylphenol found evidence of general toxicity at 200 mg/kg/d and above, and derived a NOAEL of 50 mg/kg/d. In this study pregnant dams were dosed for 10 days and repeated dose toxicity received only limited investigation. The 90-day dermal toxicity study found no evidence of systemic toxicity with 4-*tert*-pentylphenol even at the top dose of 25 mg/kg/d although local irritation was seen at 2.5 mg/kg/d and above. Bearing in mind that these two studies provide limited information on the systemic toxicity of 4-*tert*-pentylphenol, it is considered appropriate to read-across to 4-*tert*-butylphenol for repeated dose toxicity. The most sensitive repeat dose toxicity study with 4-*tert*-butylphenol was the two-generation study, which found evidence of general toxicity at 200 or 600 mg/kg/d. The NOAEL identified in this study was 70 mg/kg/d which should be taken forward to the risk characterisation as the NOAEL for repeated dose toxicity.

4.4.7 Mutagenicity

4.4.7.1 *In vitro* studies

4.4.7.1.1 Bacterial studies

Three Ames tests have been conducted with 4-*tert*-pentylphenol. The first study, conducted according to OECD guideline 471 and GLP (Hüls, 1996d), used *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without S9 metabolic activation. The test substance was used in plate incorporation assays at concentrations up to 5,000 µg/plate and in preincubation assays at concentrations up to 100 µg/plate, and gave negative results for mutagenicity. Negative results were also produced in two other studies conducted in several strains of *S. typhimurium* with and without metabolic activation (Zeiger *et al*., 1988; May, 1990).

4.4.7.1.2 Mammalian cell studies

In a mouse lymphoma gene mutation assay conducted to US EPA guidelines, 4-*tert*-pentylphenol was tested without activation at concentrations of up to 40 µg/mL and with activation at concentrations of up to 10 µg/mL (Lloyd, 1990). Although in some individual cell cultures treated with 4-*tert*-pentylphenol there was a higher incidence of mutant colonies than in controls, there was no relationship with dose and this was considered to be a chance finding related to biological variation in the control cultures.

4.4.7.2 *In vivo* studies

A micronucleus assay was conducted with 4-*tert*-pentylphenol (Edwards, 1990). The study was conducted according to US EPA guidelines, although the route of exposure was not reported in the secondary literature source. Male mice (CD-1 strain) were treated at 62.5, 250 and 1,000 mg/kg and female mice were treated at 250, 1,000 and 4,000 mg/kg. The test was negative.

4.4.7.3 Studies in humans

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.7.4 Summary of mutagenicity

From the *in vitro* and *in vivo* tests conducted, there is no evidence that 4-*tert*-pentylphenol is a gene mutagen, clastogen or aneugen. Consequently, the substance is not considered to be mutagenic.

4.4.8 Carcinogenicity

4.4.8.1 Studies in animals

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.8.2 Studies in humans

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.8.3 Summary of carcinogenicity

On the basis of the negative results in mutagenicity tests, 4-*tert*-pentylphenol is not considered to be a genotoxic carcinogen. There are no experimental data to assess whether or not 4-*tert*-pentylphenol causes cancer by non-genotoxic mechanisms. However, due to its corrosive nature, repeated exposure to high doses of 4-*tert*-pentylphenol could conceivably cause an increase in tumour incidence at the site of contact as a consequence of long-term local irritation.

4.4.9 Toxicity for reproduction

4.4.9.1 Effects on fertility

4.4.9.1.1 Studies in animals

The effects of 4-*tert*-pentylphenol on fertility have not been assessed in guideline studies, but the effects of 4-*tert*-butylphenol on fertility have been investigated in a two-generation study and a combined repeated dose/reproductive toxicity screening study. Both investigations were conducted in the rat with oral dosing schedules.

In the two-generation study, groups of Sprague-Dawley rats (24–28 per sex, dose and generation) were fed 4-*tert*-butylphenol in the diet at concentrations of 0, 800, 2,500 or 7,500 ppm , corresponding to dose levels of approximately 70, 200 or 600 mg/kg/d (Clubb & Jardine, 2006).

There was clear evidence of general toxicity in adult animals of both sexes at the top dose, shown by low body weight gain (20–32% below control) and food consumption (10–25% below control). During gestation dam body weight gain in both F_0 and F_1 generations was lower at the top two doses than in controls; the difference was 5–8% at 2,500 ppm and 22–32% at 7,500 ppm.

Sperm motility, count or morphology were unaffected by 4-*tert*-butylphenol treatment. In females oestrus cycle length, mating performance, fertility and duration of gestation were unaffected by treatment. A number of findings were reported at the top dose in both F_0 and F_1 females, including low ovarian weight (absolute weight 18–36% lower than in controls, relative weight 14–18% lower) and increased incidence of minimal or mild atrophy of the vaginal epithelium (incidence 43–58% compared with 4–5% in controls). At the top dose the incidence of F_0 females in proestrus was increased, and the incidence of metestrus was decreased; however, this may be a chance finding as similar changes were not seen in F_1 females. At the top dose the number of implantation sites per dam and litter size were decreased by 8–9% for the F_1 pups and by 20% for the F_2 pups. Also at 7,500 ppm an increase in the incidence of ovarian primordial follicles (134 ± 55 versus 79 ± 35 in controls) with a concurrent decrease in the incidence of growing follicles (64 ± 13 versus 80 ± 30 in controls) was reported in F_1 females; a similar though less pronounced effect was seen in the F_1 generation. Given the magnitude of the decrease in dam body weight gain at this dose, it is considered that the effects on number of implantation sites and litter size may be secondary to maternal toxicity. However, the mechanism of the effects on the ovary and vaginal atrophy is unclear.

In summary, this study found evidence of effects on ovarian weight, the incidence of vaginal atrophy and of primordial follicles, the number of implantation sites and litter size

at 7,500 ppm (the top dose). A NOAEL for fertility of 2,500 ppm (i.e. around 200 mg/kg/d) was identified.

In the combined repeated dose/reproductive toxicity screening study 4-*tert*-butylphenol was administered to 8-week old male and female rats (13 per dose and sex) by oral gavage at 0, 20, 60 or 200 mg/kg/d (Japanese Ministry of Health and Welfare, 1996). Dosing began in both males and females 14 days prior to mating and was continued in males for 28 days, and in pregnant females until day 4 after birth. In this study the only clear evidence of parental toxicity was seen at 200 mg/kg/d, where abnormal respiratory sounds were reported in some dams and increases in white cell count were reported in males. In summary, this study showed no effects on fertility and reproductive performance, even after treatment at 200 mg/kg/d for 28 days (males) and 39 days (females).

Although the effects of 4-*tert*-pentylphenol on fertility have not been assessed in standard guideline studies, the substance has been screened for oestrogenic activity with an *in vitro* assay and an *in vivo* uterotrophic assay. In addition, the androgenic activity of 4-*tert*-pentylphenol has been investigated *in vivo* in castrated rats in a Hershberger assay. The uterotrophic and Hershberger assays have been used for a number of years in several laboratories worldwide to screen for endocrine activity, and are currently in the process of being validated by the OECD.

The *in vitro* assay measured the binding of alkylphenols to the oestrogen receptor in rat uterine tissue (Blair *et al*., 2000). In this assay the oestrogenic activity of 4-*tert*-pentylphenol was found to be over five orders of magnitude lower than that of 17ß-oestradiol, but was of a similar order of magnitude as that of 4-*tert*-butylphenol and 4-*tert*-octylphenol.

In the *in vivo* uterotrophic assay 4-*tert*-pentylphenol was administered to 19–20-day-old female rats (Crj: CD strain; 6 per dose) by subcutaneous injection (0, 8, 200 and 600 mg/kg) once daily for 3 days, and uteri were weighed 24 hours after the final dose (Yamasaki *et al*., 2003). At 8, 40 and 200 mg/kg uterine weight was 94.5, 14.9 and 246% of negative control values respectively. By comparison, in positive control animals given 17ß-oestradiol at 2, 20 or 200 mg/kg/d uterine weight was 221, 409 and 409% of negative control values respectively (Yamasaki *et al*., 2002).

In the Hershberger assay 4-*tert*-pentylphenol (0, 50, 200 or 600 mg/kg) was administered to 8-week-old animals (Crj: CD strain; 6 per dose) by oral gavage once daily for 10 days (Yamasaki *et al*., 2003). Positive control animals were injected with testosterone propionate (0.2 mg/kg/d) subcutaneously on the same days. The study was terminated 24 hours after the final dose and the organs of the male reproductive tract (glans penis, Cowper's gland, prostate, seminal vesicles) and *bulbocavernosus*/*levator ani* muscle were weighed. None of these parameters were affected in animals given 4-*tert*-pentylphenol alone, but in positive control animals the weights of these organs were increased.

4.4.9.2 Studies in humans

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.9.3 Developmental toxicity

4.4.9.3.1 Studies in animals

In a standard prenatal developmental toxicity study, 4-*tert*-pentylphenol was administered by oral gavage to pregnant Sprague-Dawley rats (25 per dose) from gestation day 6 to 15 (Siglin, 1991). Doses were 0, 50, 200 and 500 mg/kg and dams and litters were sacrificed and examined after termination of the study on gestation day 20. There was evidence of maternal toxicity at the top two doses; the incidence of hair loss, urine stains, abnormal respiratory sounds and mucoid/soft stools were increased and body weight gain and food consumption were decreased by 10–50%, compared with controls. At the top dose of 500 mg/kg/d there was evidence of effects on offspring; the incidence of bent ribs was increased and foetal body weight was decreased by 6%. However, these effects are considered to be secondary to the significant maternal toxicity seen. The NOAEL was 50 mg/kg/d for maternal toxicity and 200 mg/kg/d for effects on development.

Regarding effects on postnatal development, there are no data available for 4-*tert*-pentylphenol. However, the two-generation study of Clubb & Jardine (2006) and the combined repeated dose/reproductive toxicity screening study of the Japanese Ministry of Health and Welfare (1996) provides information for 4-*tert*-butylphenol (see 4.4.9.1.1).

In the two-generation study rats were fed 4-*tert*-butylphenol in the diet at concentrations of 0, 800, 2,500 or 7,500 ppm, corresponding to dose levels of approximately 70, 200 or 600 mg/kg/d. The viability index for 4-day-old pups was found to be slightly lower at the top dose in F_1 pups (85% compared with 97% in controls), but this may well have been a chance finding as no such effect was seen in F_2 pups. In both F_1 and F_2 pups, body weight by the end of weaning was 29% lower at the top dose than in controls. In F_1 pups body weight at weaning was 9% lower at the middle dose than in controls, but the difference was only 3% in F_2 pups. At the top dose preputial separation was delayed by 4.3 days in F_1 males, and vaginal opening was delayed by 3.3 days in F_1 females (these parameters were not studied in the F_2 generation). The body weights attained on reaching these developmental milestones were similar in different treatment groups, and consequently the delays are considered to be secondary to retardation in pup body weight gain. Overall, a developmental NOAEL of 70 mg/kg/d was identified from this study for effects on pup growth at the top two doses.

In the combined repeated dose/reproductive toxicity screening study 4-*tert*-butylphenol had no effects on pup parameters, including viability index for 4-day-old pups, even at the top dose of 200 mg/kg/d.

4.4.9.4 Studies in humans

No information is available for 4-*tert*-pentylphenol or other alkylphenols.

4.4.9.5 Summary of toxicity for reproduction

The effects of 4-*tert*-pentylphenol on prenatal development have been investigated in a standard oral study in the rat, and a NOAEL of 200 mg/kg/d was identified for effects on development secondary to maternal toxicity. However, since the effects of 4-*tert*-pentylphenol on fertility, reproductive performance and postnatal development have not

been studied in guideline studies, these endpoints will be predicted from data obtained with 4-*tert*-butylphenol. The more comprehensive and sensitive reproductive toxicity study with 4-*tert*-butylphenol found consistent evidence of effects on ovarian weight, the incidence of vaginal atrophy and ovarian primordial follicles, the number of implantation sites and litter size at 600 mg/kg/d. Regarding effects on development, in pups body weight gain was retarded at 200 mg/kg/d and above. Overall the reproductive NOAEL for this study was 70 mg/kg/d.

The oestrogenic and androgenic activities of 4-*tert*-pentylphenol have been investigated in a series of screening studies. No potential for androgenic effects was identified in a Hershberger assay. Regarding oestrogenic effects, *in vivo* both 4-*tert*-pentylphenol and 4-*tert*-octylphenol gave positive results in the uterotrophic assay, and *in vitro* 4-*tert*-pentylphenol has an affinity for the oestrogen receptor of a similar order of magnitude to 4-*tert*-butylphenol and 4-*tert*-octylphenol. However, since neither 4-*tert*-butylphenol nor 4-*tert*-octylphenol produced oestrogenic effects in multigeneration or developmental studies, those data are not considered to be relevant to the risk characterisation.

Overall, the most sensitive study found a reproductive NOAEL of 70 mg/kg/d, based on retardation of pup growth, and this value will be taken forward to the risk characterisation for 4-*tert*-pentylphenol.

4.4.10 Derivation of $PNEC_{oral}$ for secondary poisoning

Secondary poisoning refers to the potential risks to predators that might be exposed to the substance via their food. The most appropriate data for estimating a $PNEC_{oral}$ are those from chronic dietary studies. In this case a NOAEL of 70 mg/kg/d for repeated dose and reproductive toxicity has been derived for 4-*tert*-butylphenol from a two-generation study (Clubb & Jardine, 2006).

The $PNEC_{oral}$ is calculated by converting the NOAEL to a NOEC (i.e. a concentration in mg/kg food) using a conversion factor (in this case 20) and then dividing the NOEC by an appropriate assessment factor (in this case 30). Since no NOAEL is available for 4-*tert*-pentylphenol, an additional factor of 10 is also applied as a precaution. The **$PNEC_{oral}$ is therefore 4.67 mg/kg**.

4.5 Hazard categorisation

4.5.1 Hazard classification

4-*tert*-Pentylphenol is not currently classified for either environmental or human health hazards on Annex 1 of Directive 67/548/EEC (according to both the ESIS database and the N-Class database[14]). Since there is no agreed harmonised classification, suppliers hold the responsibility to self-classify.

The suppliers' Safety Data Sheets (Sasol, 2004; Schenectady, 2005) indicate that the substance is classified as 'Corrosive' and 'Dangerous for the Environment', with the following risk phrases:

14 http://apps.kemi.se/nclass/default.asp

R34: Causes burns
R43: May cause sensitization by skin contact
R51/53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

This is consistent with the data reviewed in this report and is therefore a valid classification.

4.5.2 PBT assessment

Substances that are persistent (P), bioaccumulative (B) and toxic (T) pose a special risk to remote environments (such as the open ocean) because of their potential for long-range transport and accumulation in food chains. PEC/PNEC comparisons are not appropriate because of the unacceptably high uncertainty in predicting reliable exposure and/or effect concentrations, and the consequences in terms of the difficulty in reversing any adverse effects should they occur.

4.5.2.1 Persistence

No marine or freshwater standard simulation test data are available. However, 4-*tert*-pentylphenol is considered to be 'readily degradable, failing the 10-day window' (Section 3.1.2.2). It is therefore not persistent in the environment according to the TGD criteria.

4.5.2.2 Bioaccumulation

No experimental data for bioconcentration are available. The estimated fish BCF is 501 (Section 3.1.8), which marginally meets the Chemicals Stakeholder Forum's (CSF) criterion for a substance of concern. However, this BCF value is well below both the CSF criterion for highest concern and the TGD criterion for bioaccumulation.

4.5.2.3 Toxicity

There are no data for 4-*tert*-pentylphenol to suggest chronic aquatic toxic effects at concentrations lower than 0.01 mg/L. The substance is not classified for chronic mammalian effects. It therefore does not meet the TGD criterion for toxicity. There is some evidence to suggest that 4-*tert*-pentylphenol affects the vertebrate endocrine system, in fish at least.

4.5.2.4 Conclusion of PBT assessment

4-*tert*-Pentylphenol is not a PBT (or very persistent, very bioaccumulative 'vPvB') substance based on screening information. In particular it is not expected to persist in the environment and its bioaccumulation potential is not high enough to meet the criteria.

5 Risk characterisation

The following sections characterise risks for the aquatic, terrestrial and atmospheric compartments and the risk of secondary poisoning of predators in the food chain. The risk characterisation is performed by comparing the PECs with the PNECs to derive a risk characterisation ratio (RCR). An RCR <1 implies that any risk resulting from that level of exposure is acceptable. An RCR >1 implies a potential risk, and all such values are highlighted in bold in the following tables (RCRs are given to two significant figures).

5.1 Aquatic compartment

5.1.1 Surface water and sediment

5.1.1.1 Risk characterisation ratios

Table 5.1 summarises local RCRs for surface waters. Sediment RCRs will be the same since they are calculated using equilibrium partitioning equations.

Table 5.1 Risk characterisation for the local aquatic compartment

Life cycle stage	Description	RCR	
		Freshwater	Marine water
1	PRODUCTION	0.024	*
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	**9.0**	0.91
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	0.70	**2.5**
4	CONFIDENTIAL USE 1	**140**	**500**
5	CONFIDENTIAL USE 2 FORMULATION	0.12	0.37
5	CONFIDENTIAL USE 2	0.32	**1.1**
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	0.088	0.27
7	CONFIDENTIAL USE 3 – FORMULATION	0.031	0.057
8	CONFIDENTIAL USE 3 – USE	0.021	0.022
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	0.020	0.019
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	0.021	0.022

Note: *The production site is inland.

The RCR for both the regional freshwater and marine compartments is 0.02. It can therefore be seen that the contribution of the local release to the overall risk is very small for several scenarios.

There is a potential risk for the aquatic environment for two scenarios for freshwater and three for marine waters. Life cycle stage 4 (confidential use 1) presents a potential risk for both types of environment.

5.1.1.2 Uncertainties and possible refinements

5.1.1.2.1 Emissions

A number of uses have been identified for the substance, but actual emissions data are only available for the European production site and the main use (life cycle stage 2). Relevant measurements of 4-*tert*-pentylphenol concentrations in site effluent for life cycle stage 2 were made in October 2006 for a site located in the UK. The measured data indicate that the freshwater RCR is 2.3. Although lower than the value in Table 5.1, this site still poses a potential risk to the freshwater compartment. It is known that this site is subject to the Pollution Prevention and Control Regulations, and so further controls may be investigated locally.

Despite attempts by the suppliers to obtain better information from their customers for the other uses, none has been forthcoming and so the emissions are based on defaults that might be overly conservative. However, these other uses do not appear to be relevant to the UK at the moment. Life cycle stage 4 represents an important use that is known to take place outside the UK, but life cycle stage 5 is a somewhat uncertain scenario that is known to be declining.

5.1.1.2.2 Other factors relevant to exposure

A K_{oc} of 2,380 L/kg has been used for the risk assessment. However, as discussed in Section 3.1.4, the log K_{ow} used to estimate the K_{oc} might be an upper limit. The geometric mean of the predicted log K_{ow} values is 3.7, which is equivalent to a K_{oc} of 1,540 L/kg using the phenol QSAR provided in the TGD. A K_{oc} of 3,799 L/kg has also been predicted using molecular connectivity indices. The true K_{oc} value may therefore lie in the range 1,540–3,799 L/kg. Using the upper or lower value only changes the RCRs by a very small amount, and does not affect the conclusions.

The UK site for life cycle stage 2 is not located on the coast, and the river it discharges to is non-tidal. Nevertheless, this river reaches the sea a few kilometres downstream. The marine scenario therefore models the local concentrations that could be expected from this discharge when it reaches the estuary, using the TGD default dilution factor of 100. It is possible that more specific local information could be used to model estuarine concentrations. However, given that emissions from the site are controlled under the Pollution Prevention and Control Regulations, any further modelling may best be investigated locally.

It is not known whether a marine scenario with or without a WWTP is relevant for the other life cycle stages since there might be no sites located at the coast.

5.1.1.2.3 Effects

A $PNEC_{freshwater}$ of 2 µg/L has been used in the risk characterisation as a reasonably conservative value, using an assessment factor of 50 with a NOEC for medaka (*Oryzias latipes*). The main uncertainty concerns the sensitivity of medaka compared with other fish species, and Section 4.1.6.1 indicates that the $PNEC_{freshwater}$ could lie somewhere in the range 0.6–10 µg/L:

- Selection of a $PNEC_{freshwater}$ of 0.6 µg/L would lead to a risk for all scenarios with a current RCR of 0.3 or above. Three life cycle stages that are already a potential risk for either fresh or marine waters would present an additional concern. These are:

- life cycle stage 2 for marine water (RCR would be 3),
- life cycle stage 3 for freshwater (RCR would be 2.3), and
- life cycle stage 5 (use) for freshwater (RCR would be 1.1).

One additional scenario would become a potential risk for marine waters (life cycle stage 5, formulation), with an RCR of 1.2.

- Conversely, if the $PNEC_{freshwater}$ were 10 µg/L, life cycle stages 3 and 5 would no longer present a risk to the marine environment. There would also no longer be a risk for the UK site involved in life cycle stage 2 based on the latest monitoring results.

Should further robust data relating to fish endocrine endpoints become available in the future, then the $PNEC_{freshwater}$ could be refined. This could include information on analogues like 4-*tert*-butylphenol, but ideally the data should concern carp rather than other species. A valid chronic toxicity test with a marine species (e.g. an echinoderm or a mollusc) may also allow application of a smaller assessment factor for the saltwater PNEC.

5.1.1.2.4 Summary

Local aquatic risks in the UK are only likely to be occurring at a single site that is subject to a regulatory approval regime capable of reducing exposures further. However, further fish toxicity data could potentially remove the concern for this site altogether.

Risks may also be occurring for other uses that are understood not to take place in the UK. Better emissions data could refine the assessment for these uses, of which life cycle stage 4 is the most important.

In the absence of better release data, a guide to an 'acceptable' emission rate can be given by calculating the maximum release that would give rise to an RCR of 1 based on the following equation:

$$CRR = PNEC_{freshwater} \times FLOW \times DIL / (F_w \times 10^6)$$

where CRR = critical release rate, kg/d
$PNEC_{freshwater} = 2 \times 10^{-3}$ mg/L
F_w = fraction of substance released to water from a 'standard' WWTP (estimated by the SIMPLETREAT model as 0.267, Section 3.1.7)
FLOW = standard WWTP flow rate (2×10^6 L/d)
DIL = TGD default dilution (10)

The regional background concentration can be ignored for this purpose since it is so low. On this basis, the critical release rate would be 0.15 kg/d.

5.1.2 Wastewater treatment plant (WWTP) micro-organisms

5.1.2.1 Risk characterisation ratios

Table 5.2 shows RCRs for WWTP.

Table 5.2 Risk characterisation for WWTP

Life cycle stage	Description	RCR
1	PRODUCTION	<< 1*
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	0.013
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	7.5×10^{-3}
4	CONFIDENTIAL USE 1	**1.5**
5	CONFIDENTIAL USE 2 FORMULATION	1.1×10^{-3}
5	CONFIDENTIAL USE 2	3.4×10^{-3}
7	CONFIDENTIAL USE 3 – FORMULATION	< 0.001
8	CONFIDENTIAL USE 3 – USE	< 0.001

Note: * The exact value is excluded for reasons of confidentiality.

A potential risk is only identified for life cycle stage 4 (confidential use 1).

5.1.2.2 Uncertainties and possible refinements

Life cycle stage 4 describes an important use, but this is understood not to take place in the UK. This scenario is based entirely on defaults and so considerable refinement is possible (e.g. by measuring actual emissions at sites processing the substance in this way). The RCR is only slightly greater than 1, so emissions would not need to be much lower to remove the concern. As noted in Section 5.1.1.2.2, the true K_{oc} value may lie in the range 1,540–3,799 L/kg. Using the upper or lower value only changes the RCRs by a very small amount, and does not affect the conclusions.

5.1.2.3 Summary

No risks to WWTP are expected in a UK context.

5.2 Terrestrial **compartment**

Releases of 4-*tert*-pentylphenol to the terrestrial compartment may occur from the application of sewage sludge arising from processes that use the substance, and from atmospheric deposition.

5.2.1 Risk characterisation ratios

The RCRs for the terrestrial compartment are shown in Table 5.3.

Table 5.3 Risk characterisation for the terrestrial compartment

Life cycle stage	Description	RCR
1	PRODUCTION	5.9×10^{-3}
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	0.68
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	0.39
4	CONFIDENTIAL USE 1	**78**
5	CONFIDENTIAL USE 2 FORMULATION	0.055
5	CONFIDENTIAL USE 2	0.18
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	0.039
7	CONFIDENTIAL USE 3 – FORMULATION	6.1×10^{-3}
8	CONFIDENTIAL USE 3 – USE	< 0.001
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	< 0.001
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	< 0.001

A potential risk is only identified for life cycle stage 4 (confidential use 1). The RCR for regional soil is 4.2×10^{-4}, and so the regional background concentration makes an insignificant contribution to the risk.

5.2.2 Uncertainties and possible refinements

As for WWTP (Section 5.1.2), the only risk arises for a use that is understood not to take place in the UK. It is based entirely on defaults, and so considerable refinement is possible (e.g. better information on emissions and sludge spreading practice for the sites involved).

The $PNEC_{soil}$ is only a screening value, based on the equilibrium partitioning method. It could be refined with actual data on soil organism toxicity (e.g. a reproduction study with an earthworm or springtail). In the absence of such data, the $PNEC_{soil}$ will also be sensitive to any changes in the $PNEC_{freshwater}$. As discussed in Section 5.1.1.2.3, this could range from 0.6 to 10 µg/L. Selection of a $PNEC_{freshwater}$ of 0.6 µg/L would have only limited consequences for the assessment, with just two life cycle stages becoming a concern that currently are not (life cycle stage 2, where the RCR would become 2.3, and life cycle stage 3, with an RCR of 1.3). Nevertheless, this approach may overestimate the risk for soil organisms, since the PNEC would be based on endocrine effects in fish that may not be relevant for soil organisms, especially given the degradable nature of the substance (meaning that long-term exposures are unlikely). Conversely, a $PNEC_{freshwater}$ of 10 µg/L would reduce the RCR for life cycle stage 4 to 16 (i.e. a risk would still be identified).

As noted in Section 5.1.1.2.2, the true K_{oc} value may lie in the range 1,540–3,799 L/kg. Using the upper or lower value only changes the RCRs by a very small amount, and does not affect the conclusions. Variation in the K_{oc} also affects the equilibrium partitioning approach, but this is not considered further in this analysis.

5.2.3 Summary

No risks to soil are currently expected in a UK context. The conclusions for other uses that take place outside the UK depend on a number of assumptions that could be refined with more reliable data on both exposure and toxicity.

5.3 Atmospheric compartment

No effect data are available for non-mammalian species that can be used to derive a PNEC. Abiotic effects are not expected. Although the lack of toxicity data for suitable species cannot be taken as implying no concern, there is unlikely to be a risk for this compartment because air concentrations are predicted to be relatively low.

5.4 Food chain risks (secondary poisoning)

5.4.1 Risk characterisation ratios

Predators may be exposed to the substance in their diet. The RCRs for simple aquatic and terrestrial food chains are shown in Table 5.4.

Table 5.4 Risk characterisation for secondary poisoning

LCS	Description	RCR			
		Freshwater fish food chain	Marine fish food chain	Marine top predators	Earthworm food chain
1	PRODUCTION	< 0.001	-	-	< 0.001
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	0.027	< 0.001	< 0.001	0.0011
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	0.0017	< 0.001	< 0.001	< 0.001
4	CONFIDENTIAL USE 1	0.40	0.15	0.029	0.11
5	CONFIDENTIAL USE 2 FORMULATION	0.0011	< 0.001	< 0.001	< 0.001
5	CONFIDENTIAL USE 2	0.0022	< 0.001	< 0.001	< 0.001
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	0.0011	< 0.001	< 0.001	< 0.001
7	CONFIDENTIAL USE 3 – FORMULATION	< 0.001	< 0.001	< 0.001	< 0.001
8	CONFIDENTIAL USE 3 – USE	< 0.001	< 0.001	< 0.001	< 0.001
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	< 0.001	< 0.001	< 0.001	< 0.001
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	< 0.001	< 0.001	< 0.001	< 0.001

No risks are identified for any part of the life cycle.

5.4.2 Uncertainties and possible refinements

As noted in Section 5.1.1.2.2, the true K_{oc} value may lie in the range 1,540–3,799 L/kg. Using the upper or lower value only changes the RCRs by a very small amount, and does not affect the conclusions.

The substance is expected to be degraded fairly rapidly in the environment and it is only moderately bioaccumulative. It is therefore not too surprising that predicted concentrations in fish and worms are relatively low. The selected fish BCF value may be conservative. Several scenarios are also based on conservative default release estimates, and these are refinable with better information on emissions.

In addition, the $PNEC_{oral}$ is calculated from toxicity data for 4-*tert*-butylphenol using an additional uncertainty factor of 10 as a precaution since relevant data are not available for

the substance itself. If such data were to become available in the future, the $PNEC_{oral}$ could be revised.

5.4.3 Summary

No food chain risks are expected for this substance based on its current use pattern.

5.5 Risks to human health following environmental exposure

4-*tert*-Pentylphenol lacks mutagenic potential and is not expected to cause cancer by a genotoxic mechanism. The critical NOAEL is 70 mg/kg/d for repeated dose and reproductive toxicity obtained in a rat multigenerational study with 4-*tert*-butylphenol. Margins of Safety (MoS) between the predicted exposures and the NOAEL for the various life cycle stages are summarised in Table 5.5.

Table 5.5 Risk characterisation for humans exposed via the environment (total exposure)

Life cycle stage	Description	Margin of Safety
1	PRODUCTION	3.4×10^5
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	1.5×10^4
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	1.4×10^5
4	CONFIDENTIAL USE 1	630
5	CONFIDENTIAL USE 2 FORMULATION	3.8×10^5
5	CONFIDENTIAL USE 2	1.6×10^5
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	4.2×10^5
7	CONFIDENTIAL USE 3 – FORMULATION	1.7×10^6
8	CONFIDENTIAL USE 3 – USE	1.9×10^6
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	2.0×10^6
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	1.9×10^6

The predicted total daily intake by the oral route for regional exposure is 3.6×10^{-5} mg/kg/d.

A lowest acceptable MoS of 200 can be calculated by multiplying the following individual assessment factors, as described in the TGD: 10 for intraspecies differences, 10 for interspecies differences and 2 for extrapolating from sub/semi-chronic to chronic exposure.

The lowest MoS is for life cycle stage 4 (confidential use 1). Since this is greater than 200, there are no concerns for human health for any scenario.

As noted in Section 5.1.1.2.2, the true K_{oc} value may lie in the range 1,540–3,799 L/kg. Using the upper or lower value only changes the RCRs by a very small amount, and does not affect the conclusions.

6 Conclusions

4-*tert*-Pentylphenol is mainly used as a chemical intermediate in Europe for several applications, particularly phenolic resins. This is the only part of the life cycle (stage 2) known to occur in the UK.

No risks are expected for air, secondary poisoning of predators or human health following environmental exposure for any stage of the life cycle. The potential risks for the remaining risk assessment protection goals are highlighted in Table 6.1 (actual risk characterisation ratios may be found in Section 5).

Table 6.1 Life cycle stages that flag as potential risks in this assessment

LCS	Description	Potential risks			
		Freshwater compartment	Marine aquatic compartment	WWTP micro-organisms	Soil organisms
1	PRODUCTION	-	-	-	-
2	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 1	▲	-	-	-
3	SYNTHETIC INTERMEDIATE FOR PHENOLIC RESINS, SITE TYPE 2	-	▲	-	-
4	CONFIDENTIAL USE 1	▲	▲	▲	▲
5	CONFIDENTIAL USE 2 FORMULATION	-	-	-	-
5	CONFIDENTIAL USE 2	-	▲	-	-
6	OILFIELD – USE – LOSS OF UNREACTED 4-*tert*-pentylphenol	-	-	-	-
7	CONFIDENTIAL USE 3 – FORMULATION	-	-	-	-
8	CONFIDENTIAL USE 3 – USE	-	-	-	-
9	CONFIDENTIAL USE 3 – SERVICE LIFE – LOSS OF UNREACTED 4-*tert*-pentylphenol	-	-	-	-
10	CONFIDENTIAL USE 3 – DISPOSAL – LOSS OF UNREACTED 4-*tert*-pentylphenol	-	-	-	-

It can be seen that life cycle stages 1, 6, 7, 8, 9 and 10 (i.e. production, use of phenolic resins in oil recovery and confidential use 3) do not give rise to any risks based on the current assumptions.

The highest RCRs are identified for life cycle stage 4 (confidential use 1) – this is a significant European use, but is understood not to take place in the UK. Three further life cycle stages (2, 3 and 5) present less significant potential risks, with RCRs ranging from 1.1 to 2.5. Only one of these (life cycle stage 2) is known to take place in the UK, and local aquatic risks are only likely to be occurring at a single site that is subject to a regulatory approval regime capable of reducing exposures further.

The main areas of uncertainty associated with this assessment are:

- *The reliability of default release assumptions*. The potential risks for life cycle stages 3 and 5 could probably be removed with better emissions data, and those for life cycle stage 4 could be refined significantly. A release rate < 0.15 kg/d would not be expected to give rise to an aquatic risk based on the data currently available.

- *The choice of fish toxicity data (and associated uncertainty factor) on which to base the* $PNEC_{freshwater}$. Ideally, further investigation of effects

on common carp *Cyprinus carpio* reproduction and growth should be performed using robust experimental techniques (e.g. in a life cycle test). Additional data on analogues like 4-*tert*-butylphenol could also be useful. If the resulting $PNEC_{freshwater}$ became as high as 10 µg/L, only life cycle stage 4 would remain a risk. Conversely, confirmation of effects on carp at low concentrations could result in a $PNEC_{freshwater}$ around 0.6 µg/L, in which case aquatic risks would be identified for several more scenarios (although these would still be refinable with better emissions data).

The uncertainty over the choice of K_{oc} makes little overall difference to the conclusions. A valid chronic toxicity test with a marine species (e.g. an echinoderm or a mollusc) may also allow application of a smaller assessment factor for the saltwater PNEC.

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8 Glossary of terms

Term	Description
Bioconcentration factor (BCF)	A measure of chemical uptake, being the ratio between the concentration in an organism and the concentration in an environmental compartment (usually water)
CAS number (no.)	An identifying code number assigned to chemicals by the Chemical Abstract Services. The CAS number is a generally recognised identification reference for a chemical; it is possible that a substance can have more than one such number
Lowest observed effect concentration	The lowest concentration in a toxicity test that gives rise to adverse effects (relative to a control)
Median effective concentration (EC_{50})	The concentration in a toxicity test at which a particular effect is observed in half of the organisms exposed for a specified time
Median lethal concentration/dose (LC/D_{50})	The concentration in a toxicity test that can be expected to cause death in half of the organisms exposed for a specified time
No observed effect concentration (NOEC)	The highest concentration in a toxicity test that does not give rise to adverse effects (relative to a control)
n-Octanol–water partition coefficient (K_{ow})	This parameter gives an indication of the partitioning behaviour of a substance between water and lipid-containing materials such as cell membranes or organic matter in soils and sediments
Organic carbon–water partition coefficient (K_{oc})	This parameter gives an indication of the partitioning behaviour of a substance between water and organic matter in soils, sediments and sewage sludge
Readily biodegradable	Rapid environmental degradation to carbon dioxide and water, etc., as measured by laboratory screening tests involving micro-organisms

9 Abbreviations and acronyms

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Services
CSF	Chemicals Stakeholder Forum
d	Day
DIN	Deutsche Industrie Norm (German test method)
DOC	Dissolved organic carbon
EA	Environment Agency
EC	European Communities
EC_{50}	Median effect concentration
EC_x	As EC_{50}, but for x% effect; x usually being 0, 10 or 100
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances – this lists all chemical substances that were supplied to the market prior to 18 September 1981
EPA	Environmental Protection Agency (USA)
ER	Oestrogen reception
ESIS	European Chemical Substances Information System
ESR	The Existing Substances Regulation – Council Regulation (EEC) 793/93 on the evaluation and control of the risks of 'existing' substances
EU	European Union
EUSES	European Union System for the Evaluation of Substances (software tool in support of the TGD on risk assessment)
F_0	Parent generation
F_1	First filial generation
F_2	Second filial generation
GLP	Good laboratory practice
h	Hour
HLC	Henry's Law constant
HPV	High Production Volume (supply >1,000 tonnes/year)
ICCA	International Council of Chemical Associations
IUPAC	International Union for Pure and Applied Chemistry – the IUPAC name is the formal chemical name
km	Kilometre
K_{oc}	Organic carbon normalised distribution coefficient
K_{ow}	Octanol–water partition coefficient
Kp	Solids–water partition coefficient
L/EC_{50}	Median lethal/effect concentration
LCS	Life cycle stage
LC/D_{50}	Median lethal concentration/dose
LOEC	Lowest observed effect concentration
LO(A)EL	Lowest observed (adverse) effect level
MATC	Maximum Acceptable Toxic Concentration
mg/kg/d	Milligrams per kilogram per day
mmHg	Millimetres of mercury, a measure of pressure.
MW	Molecular weight
NOEC	No observed effect concentration
NO(A)EL	No observed (adverse) effect level
n.t.p.	Normal temperature and pressure (20°C and 101.3 kPa)

OECD	Organisation for Economic Co-operation and Development
O.J.	Official Journal of the European Communities
PBT	Persistent, bioaccumulative and toxic
PEC	Predicted environmental concentration
pH	Logarithm (to the base 10) of the hydrogen ion concentration [H^+]
pKa	Logarithm (to the base 10) of the acid dissociation constant
PNEC	Predicted no-effect concentration
(Q)SAR	(Quantitative) Structure–Activity Relationship
RBA	Relative binding affinity
RCR	Risk characterisation ratio
SDS	Safety Data Sheet
SMILES	Simplified Molecular Input Line Entry System – the SMILES code is a chemical notation system used to represent a molecular structure by a linear string of symbols; it is a simple way of entering chemical structural information into a computer program
TGD	Technical guidance document
US EPA	United States Environmental Protection Agency
vPvB	Very persistent and very bioaccumulative
wt	Weight
WWTP	Wastewater treatment plant

APPENDIX 1

Ecotoxicological properties of other related alkylphenols

In-depth risk evaluations have been performed in Europe for 4-*tert*-butyl-, 4-*tert*-pentyl-, 4-*tert*-octyl- and 4-nonylphenol (SFT, 2007; this report; EA, 2005b; EC, 2002). This appendix summarises the available information for the other two substances within this series, 4-hexylphenol and 4-heptylphenol. Neither substance appears to be supplied in Europe in commercially important amounts according to the ESIS database (i.e. no company reported supplying either substance above 10 tonnes/year in the early 1990s).

The main CAS numbers for these substances indicate that they have linear *n*-alkyl (rather than branched *tertiary*-alkyl) chains, but it is not always clear which isomers the available data apply to. Consequently, all available data are reported below. A thorough literature search has not been performed.

A1.1 4-Hexylphenol

A1.1.1 Identification of the substance

CAS number: 2446-69-7

EINECS number: 219-501-2

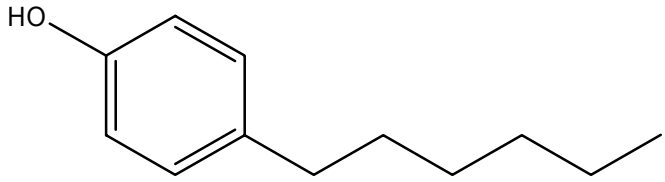
IUPAC name: 4-*n*-hexylphenol

EINECS name: *p*-hexylphenol

Molecular formula: $C_{12}H_{18}O$

Structural formula:

Figure A1.1 Structure of 4-*n*-hexylphenol



SMILES code: Oc(ccc(C1)CCCCCC)c1

Synonyms (TOXNET, 2005) : 4-*n*-hexylphenol
p-*n*-hexylphenol
phenol, *p*-hexyl-

A1.1.2 Available data

Data on physico-chemical properties and environmental fate and behaviour for 4-hexylphenol are reported in Tables A1.1–A1.2. This substance is not included in a recent US EPA review of alkylphenols (US EPA, 2007c).

Table A1.1 Summary of physico-chemical properties for 4-hexylphenol

Property	Value	Reference
Molecular weight	178.28 g/mole	
Melting point	70°C (calculated)	Mean value from MPBPWIN v1.41
Boiling point	281°C (calculated)	Estimated by MPBPWIN v1.41
Vapour pressure	0.46 Pa (calculated)	MPBPWIN v1.41
Water solubility (at 25°C)	29.7 mg/L (calculated)	Estimated by WSKOW v1.41
n-Octanol–water partition coefficient (K_{ow})	4.52 (calculated)	Estimated by KOWWIN v1.67
	3.6 (measured)	McCleese *et al*., 1981

Note: The reference for all models is US EPA, 2007a.

It should be noted that some of these values may not be very reliable (especially the vapour pressure and the measured K_{ow} by comparison with 4-*tert*-pentylphenol).

Table A1.2 Summary of environmental fate data for 4-hexylphenol

Property	Value	Reference
Biodegradability	Biodegrades in weeks	Estimated by BIOWIN v4.02.
Photodegradation	$t_{½}$ = 2.7 h (calculated)	Estimated by AOPWIN v1.91
Bioconcentration factor (BCF)	598	Estimated by BCFWIN v2.15
	592 ± 174	Sundt & Baussant, 2003

Note: The reference for all models is US EPA, 2007a.

These properties are very similar to those for 4-*tert*-pentylphenol.

Only two measured ecotoxicity results were found in the literature:

- A 96-h LC_{50} of 0.90 mg/L for the bay shrimp *Crangon septemspinosa* using a static renewal regime (McLeese *et al*., 1981). This study is judged to be reliable with restrictions.

- A 5-h EC_{50} of 4.50 mg/L for mobility for the terrestrial nematode *Caenorhabditis elegans* (L1 larval stage) (Tominaga *et al*., 2003). Again, this study is judged to be reliable with restrictions.

No standard toxicity data appear to be available for fish, *Daphnia* or algae. This is commented upon further in Section A1.3.

A1.2 4-Heptylphenol

A1.2.1 Identification of the substance

CAS number: 1987-50-4 and 72624-02-3

EINECS number: 217-862-0 and 276-743-1

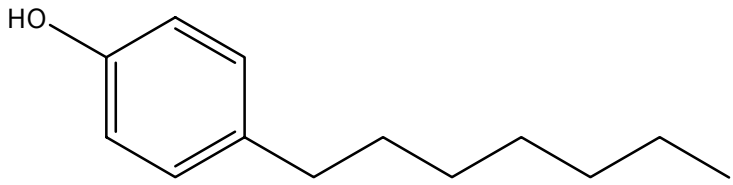
IUPAC name: 4-heptylphenol

EINECS name: 4-heptylphenol and 'Phenol, heptyl derivs'

Molecular formula: $C_{13}H_{20}O$

Structural formula:

Figure A1.2 Structure of 4-*n*-heptylphenol



SMILES code: Oc(ccc(C1)CCCCCCC)c1

Synonyms (TOXNET, 2005) : 4-*n*-heptylphenol
p-heptylphenol
p-hydroxyheptylbenzene
phenol, 4-heptyl-

A1.2.2 AVAILABLE DATA

Data on physico-chemical properties and environmental fate and behaviour for 4-heptylphenol are reported in Tables A1.3–A1.4. This substance has been assessed under the US EPA's HPV Challenge Program, and so where data have been cited as HERTG (2006) or US EPA (2007c) no further analysis has been performed for the purposes of this assessment.

Table A1.3 Summary of physico-chemical properties for 4-heptylphenol

Property	Value	Reference
Molecular weight	192.3 g/mole	
Melting point	73°C (estimated)	US EPA, 2007c
	< – 5°C	HERTG, 2006
Boiling point	256–280°C (measured)	US EPA, 2007c; HERTG, 2006
Vapour pressure	0.0113 hPa at 25°C	US EPA, 2007c
	0.0113 mmHg at 25°C	HERTG, 2006
Water solubility	122 mg/L at 25°C	US EPA, 2007c
	12.2 mg/L (shake flask method)	HERTG, 2006
n-Octanol–water partition coefficient (K_{ow})	4.5 (experimental)	Tollefsen *et al*., 1998 (cited in HERTG, 2006)
	5.01 (estimated)	US EPA, 2007c

Note: There are unexplained discrepencies between the two main references. For example, HERTG (2006) states that the substance is a liquid, but US EPA (2007c) gives a melting temperature that suggests it is a solid. Some of the units also differ where the same numerical value has been cited (e.g. vapour pressure and water solubility).

Table A1.4 Summary of environmental fate data for 4-heptylphenol

Property	Value	Reference
Biodegradability	Not readily biodegradable (estimated)	US EPA, 2007c
	25% degradation after 28 d (OECD Test Guideline 301B using adapted inoculum)	HERTG, 2006
	~40% biodegradation in seawater over 28 d	HERTG, 2006
Photodegradation	$t_{½}$ = 2.6 h (calculated)	HERTG, 2006
Bioconcentration factor (BCF)	1,429	Estimated by BCFWIN v2.15
	520 ± 197	Sundt & Baussant, 2003

4-Heptylphenol is expected to be less biodegradable than 4-*tert*-pentylphenol. Its bioaccumulation potential seems to be similar, or slightly higher.

The following measured ecotoxicity results were found in the literature:

- *Fish*

  - A 96-h LC_{50} of 0.56 mg/L for juvenile Atlantic cod *Gadus morhua* (Tollefsen *et al*., 1998) using a flow-through system at a temperature of 9.7°C, an oxygen saturation of 89%, salinity of 32.7‰ and pH of 8.1. Again, this study is judged to be reliable with restrictions (the test

concentrations were not confirmed analytically). The test substance purity was ≥97%.

- US EPA (2007c) report a 96-h LC_{50} of 0.85 mg/L for rainbow trout *Oncorhynchus mykiss* (no further reference or validity marking is given).

- *Aquatic invertebrates*

  - HERTG (2006) report a 48-h *Daphnia magna* EC_{50} of 0.38 mg/L. This study is judged to be reliable without restriction by this source.

  - A 96-h LC_{50} of 0.60 mg/L for the bay shrimp *Crangon septemspinosa* using a static renewal regime (McLeese *et al*., 1981). This study is judged to be reliable with restrictions.

- *Algae*

  - HERTG (2006) report a 72-h E_rC_{50} of 1.2 mg/L (and a 72-h NOEC of 0.048 mg/L) for the alga *Scenedesmus subspicatus*. This study is judged to be reliable without restriction by this source. In contrast, US EPA (2007c) report a 96-h E_rC_{50} of 2.5 mg/L for this species (no further reference or validity marking is given).

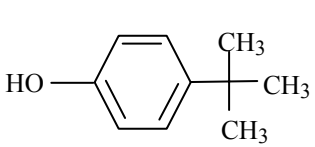
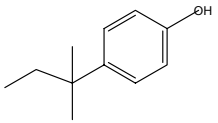
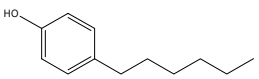
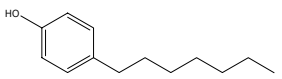
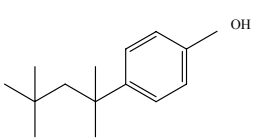
- *Terrestrial invertebrates*

  - A 5-h EC_{50} of 1.53 mg/L for mobility for the terrestrial nematode *Caenorhabditis elegans* (L1 larval stage) (Tominaga *et al*., 2003). Again, this study is judged to be reliable with restrictions because the test concentrations were not confirmed analytically (and the test substance purity was not indicated).

A1.3 Other considerations

A detailed estimate of actual toxicity values for fish, *Daphnia* and algae for 4-hexylphenol is outside the scope of this report. However, Table A1.5 presents relevant data for substances at both ends of the series so that trends can be seen (physico-chemical data are presented in Appendix 3). As expected, toxicity increases with increasing molecular weight (and hence hydrophobicity). As a worst case it could be assumed that 4-hexylphenol would be classifiable as very toxic to aquatic organisms (i.e. acute $L(E)C_{50}$ < 1 mg/L) with the potential to cause long-term adverse effects in the aquatic environment (due to its presumed persistence and/or bioaccumulation potential).

Table A1.5 Comparison of valid measured ecotoxicity data for C_4–C_8 alkylphenols

Trophic level	Concentration, µg/L				
	4-*tert*-butylphenol[a]	4-*tert*-pentylphenol	4-hexylphenol	4-heptylphenol	4-*tert*-octylphenol[b]
					
Fish[c]					
Acute *Pimephales promelas* 96-h LC_{50} (freshwater)	5,100	2,500	-	560–850 (other species)	290
Chronic fish (freshwater) *Oryzias latipes*	-	100 µg/L ($60\text{-d NOEC}_{reproduction}$)	-	-	4.3[d] (full life cycle test NOEC)
Invertebrates[c]					
Acute *Daphnia magna* 48-h EC_{50} (freshwater)	5,000	1,800	-	380	270
Chronic *Daphnia magna* 21-d NOEC (freshwater)	730	-	-	-	62
Acute *Crangon septemspinosa* 96-h LC_{50} (saltwater)	1,900	1,700 µg/L	900	600	420 (48-h LC_{50} *Acartia tonsa*)
Algae[c]					
Pseudokirchneriella subcapitata 96-h E_rC_{50} (freshwater)	14,000	4,200	-	1,200 (*Scenedesmus subspicatus*)	1,900[e]

Note: a – Data taken from SFT (2007).
b – Data taken from EA (2005b).
c – It should be noted that other species may be more sensitive than the ones shown here, e.g. the 96-h EC_{50} for the freshwater invertebrate *Gammarus pulex* is 13 µg/L for 4-*tert*-octylphenol. However, single species are preferred to illustrate the general trend. Data for other species are given where the main species has not been tested for a specific substance.
d – This result was not available when the risk evaluation of 4-*tert*-octylphenol was finalised. The reference is Japanese Ministry of the Environment (2006). Only the text for the results tables are available in English, but the test was conducted by a government laboratory and so is assumed to be valid. This NOEC is for the presence of vitellogenin in males in both the F_0 and F_1 generations. Of the endpoints that are more usually associated with adverse chronic effects, the lowest NOEC was 30.4 µg/L for the number of eggs and % fertility in the F_0 generation. For comparison, a 60-d $NOEC_{growth}$ of 6.1 µg/L was reported for *Oncorhynchus mykiss*.
e – No fully valid algal study is available for 4-*tert*-octylphenol – this result is classed as 'use with care'.

APPENDIX 2

Example quality assessment sheet using the Australasian Ecotoxicology Database system

This appendix illustrates the use of the Australasian Ecotoxicology Database quality scoring system. All ecotoxicity studies were scored using this system, which is attractive since it permits a more quantitative approach. However, it was found that the scores did not provide much additional value for the analysis compared to the traditional Klimisch system, so the actual scores are not given in the main report. Further details are available on request. The example is for the following study:

> Davoren M & Fogarty AM, 2005. Ecotoxicological evaluation of the biocidal agents sodium *o*-phenylphenol, sodium *o*-benzyl-*p*-chlorophenol, and sodium *p*-tertiary amylphenol. *Ecotoxicology and Environmental Safety*, **60**, 203–212.

Quality criteria	Details in reference	Possible score	Score awarded
Exposure duration (e.g. 48 or 96 h)	*Vibrio fischeri*: 15 min *Pseudokirchneriella subcapitata*: 96-h *Tetrahymena thermophilia*: 24-h *Thamnocephalus platyurus*: 24-h *Artemia salina*: 24-h *Daphnia magna*: 48-h *Oncorhynchus mykiss*: 96-h	10 or 0	10

Quality criteria	Details in reference	Possible score	Score awarded
Biological endpoint (e.g. immobilisation or population growth)	*Vibrio fischeri*: light inhibition	10, 5	10
	Pseudokirchneriella subcapitata: population growth	(if endpoint only stated & not defined), or 0	
	Tetrahymena thermophilia: population growth		
	Thamnocephalus platyurus: survival		
	Artemia salina: survival		
	Daphnia magna: survival		
	Oncorhynchus mykiss: survival		
Biological effect (e.g. LC or NOEC)	*Vibrio fischeri*: EC_{50} = 30 µg/L	5 or 0	5
	Pseudokirchneriella subcapitata: EC_{10} = 2100, EC_{50} = 4200, NOEC = 3200 µg/L		
	Tetrahymena thermophilia: EC_{10} = 1100, EC_{50} = 4500, NOEC = 1800 µg/L		
	Thamnocephalus platyurus: LC_{10} = 1300, LC_{50} = 2100, NOEC = 1000 µg/L		
	Artemia salina: LC_{10} = 3800, LC_{50} = 6500, NOEC = 1000 µg/L		
	Daphnia magna: EC_{10} = 2200, EC_{50} = 2700, NOEC = 1600 µg/L		
	Oncorhynchus mykiss: LC_{10} = 300, LC_{50} = 1000, NOEC = 180 µg/L		
Biological effect quantification (e.g. 50% or 25% effect)	Yes	5 or 0	5
Appropriate controls (e.g. no toxicant and/or solvent controls)	Undosed and methanol controls	5 or 0	5
Replication of each control and chemical concentration (at least duplicates)	Not reported, but standard guidelines were followed	5 or 0	5

Quality criteria	Details in reference	Possible score	Score awarded
Test acceptability criteria (e.g. acceptable level of control mortality). Note: invalid data must not be used.	All tests performed according to OECD, British Standard, or manufacturers' guidelines	5, 2 (if acceptability criteria inferred because test method (e.g. OECD) uses validation criteria), or 0	2
Test organism characteristics (e.g. length, mass, age)	*Vibrio fischeri*: Microtox kit *Pseudokirchneriella subcapitata*: algae (CCAP 278/4) in exponential growth *Tetrahymena thermophilia*: Protoxkit F from Alcontrol Ltd, UK *Thamnocephalus platyurus*: Thamnotoxkit F F from Alcontrol Ltd, UK *Artemia salina*: cysts from Galway Aquatic Ltd, Ireland *Daphnia magna*: from US EPA Cincinnati, cultured in the laboratory *Oncorhynchus mykiss*: 0+ fry from Central Fisheries Board, Ireland.	5 or 0	5
Test medium type	*Vibrio fischeri*: Microtox reagent (saline) *Pseudokirchneriella subcapitata*: APHA (1995) algal growth medium *Tetrahymena thermophilia*: freshwater medium (provided in kit) *Thamnocephalus platyurus*: freshwater medium (provided in kit) *Artemia salina*: not stated *Daphnia magna*: BS EN ISO 6341 (1996) reconstituted water *Oncorhynchus mykiss*: dechlorinated tap water	5 or 0	5

Quality criteria	Details in reference	Possible score	Score awarded
Exposure type (e.g. static, semi-static or flow-through)	All static, except for *Oncorhynchus mykiss*, which was semi-static (24-h renewal)	4 or 0	4
Chemical concentrations measured?	No	4 or 0	0
Parallel reference toxicity tests run?	Yes	4 or 0	4
Concentration-response observable or stated?	Yes	4 or 0	4
Appropriate statistical methods or model used for analysis?	Yes	4 or 0	4
For NOEC/LOEC/MATC data was significance level $\leq$0.05?	Yes	4 or 0	4
OR			
For LC/EC data was estimate of variability provided?			
For metals tested in freshwater were the following parameters measured? pH, hardness, alkalinity, organic carbon	Not applicable	3, 1 or 0	-
For all other chemicals (non-metals), was pH measured and reported?	No (or not relevant for saltwater tests)	3, 1 or 0	0 or -
For saltwaters (marine or estuarine) was salinity/conductivity measured and reported?	No	3 or 0	0
For tests not using aquatic macrophytes and algae, was the dissolved oxygen content of the water measured during the test?	No, except for *O. mykiss* (>60% saturation)	3 or 0	0
Was temperature measured and reported?	Yes – for room or incubator	3, 1 (if room/chamber settings stated), or 0	1
Were analytical reagent grade chemicals or similar used?	Yes – obtained from Ceva Sante Animale, France	3 or 0	3

Quality criteria	Details in reference		Possible score	Score awarded
TOTAL SCORE		**76** (**79 for *O. mykiss***)		
Total possible scores:	FW/metal/non-plant = 100 FW/non-metal/non-plant = 91 FW/metal/plant = 97 FW/non-metal/plant = 88 Saltwater/non-plant = 91 Saltwater/plant = 88			
AED QUALITY SCORE ([Total score/total possible score] *100)		*V. fischeri*: 86.4% *P. subcapitata*: 86.4% *T. thermophilia*: 83.5% *T. platyurus*: 83.5% *A. salina*: 83.5% *D. magna*: 83.5% *O. mykiss*: 86.8%		
AED QUALITY CLASS (High ≥80%, Acceptable 51–79%, Low ≤50%)				**High**
KLIMISCH CODE (for comparison)				2

APPENDIX 3

Predicting mammalian toxicity from data for other alkylphenols

A3.1 Introduction

The mammalian toxicity of 4-*tert*-pentylphenol has not been adequately investigated. In particular, there are no toxicokinetic data and the repeated dose and reproductive toxicity data are limited. However, other alkylphenols with a close structural relationship (notably 4-*tert*-butylphenol, 4-*tert*-octylphenol and nonylphenol) have been more extensively tested. This offers the possibility of predicting the toxic properties of 4-*tert*-pentylphenol in the data gap areas from what is known about the toxicity of these well-tested alkylphenols.

To determine if such a read-across approach is justified, as a first step, the physico-chemical, toxicokinetic and toxicological properties of alkylphenols in the C_4–C_9 series will be assessed together, looking for similarities between the group members and relationships between structure and toxicity within the series. Secondly, the selection of read-across data for toxicokinetics, repeated dose toxicity and reproductive toxicity will be discussed.

A3.2 Assessment of the toxicological properties of the C_4–C_9 alkylphenol series: suitability for read-across

The available physico-chemical, toxicokinetic and toxicity data are summarised, with references to key data, in Tables A3.1 and A3.2. (Structural diagrams are provided in Appendix 1.) Note that some of the references for 4-*tert*-octylphenol are additional to those provided in EA (2005b).

A3.2.1 Physico-chemical properties

The alkylphenols for which physico-chemical data are available are all hydrophobic (log K_{ow} >3) and weakly acidic (pK_a >10). Water solubility decreases with increasing alkyl chain length.

A3.2.2 Toxicokinetics

Toxicokinetics studies have been carried out for 4-*tert*-butylphenol, 4-*tert*-octylphenol and nonylphenol, with nonylphenol being the most comprehensively studied. From oral dosing studies in the rat it is evident that 4-*tert*-butylphenol and nonylphenol are extensively (>50%) absorbed from the gastrointestinal tract, and both 4-*tert*-octylphenol and nonylphenol were distributed to the liver, kidney, skeletal muscle and brain. The lipophilicity of alkylphenols suggests that after high exposures the adipose tissue might act as a site of deposition, particularly with longer chain alkylphenols. There is evidence that all three alkylphenols are metabolised to glucuronide and sulphate conjugates in the liver. Although a study with a straight-chain nonylphenol (4-*n*-nonylphenol) demonstrated significant oxidation of the alkyl chain, this pathway is expected to be less active with branched-chain alkylphenols.

Table A3.1 Physico-chemical and acute toxicity data for C_4–C_9 alkylphenols

Substance	CAS no. Mol wt	Physico-chemical properties	Toxicokinetic data	Acute toxicity (LD_{50} or LC_{50})			Skin irritation	Eye irritation	Skin sensitisation
				Oral	Dermal	Inhalation			
4-*tert*-Butylphenol (SFT 2007)	98-54-4 MW 152	Log K_{ow} 3.3 Water sol. 600 mg/L pKa 10.16	*In vivo* oral, iv (rat) Extent of oral abs >73 %	>2000 mg/kg (Klonne *et al*. 1988)	>2000 mg/kg (Klonne *et al*. 1988)	>5.6 mg/L/4 h (Klonne *et al*. 1988)	Corrosive (Sandoz 1991; Klonne *et al*. 1988; Hüls 1985; Schenectady 1982)	Severe irritation (Klonne *et al*. 1988)	Negative (two M & K) (Hüls 1998; Zimerson *et al*. 1999)
4-*tert*-Pentylphenol (this report)	80-46-6 MW 164	Log K_{ow} 4.0 Water sol. 168 mg/L pKa 10.43	No data	>2000 mg/kg (Hüls 1995c)	No data	No data	Corrosive (Hüls 1998; Safepharm 1991)	No data	Positive (Buhler) (Hüls 1996c)
4-*n*-Hexylphenol	2446-69-7 MW 178	Log K_{ow} 3.6–4.5 Water sol. 180 mg/L	No data	No data	No data	No data	No data	No data	No data
4-*n*-Heptylphenol (see Appendix 1)	1987-50-4 MW 192	Log K_{ow} 4.5–5.0 Water sol. 12.2 mg/L	No data	No data	No data	No data	No data	No data	No data
4-Heptylphenol	72624-02-3 MW 192	No data	No data	200–2000 mg/kg (Biosearch 1982a)	>2000 mg/kg (Biosearch 1982b)	No data	Irritation (Biosearch 1982a)	Irritation (Biosearch 1982a)	No data
4-*tert*-Octylphenol (EA 2005b)	140-66-9 MW 206	Log K_{ow} 4.1 Water sol. <20 mg/L pKa 10.33	*In vivo* oral, iv (rat)	>2000 mg/kg (Safepharm 1991)	>2000 mg/kg (BASF 1981)	<116 mg/L/1 h (Röhm & Haas 1973)	Irritation (Hüls 1984; Safepharm 1991)	Severe irritation (Hüls 1984; Safepharm 1991)	Negative (M & K) (Hüls 1988a)
Nonylphenol mixed isomers & 4-nonylphenol (branched) (EC 2002)	84852-15-3 & 25154-52-3 MW 220	Log K_{ow} 4.5 Water sol. <11 mg/L	*In vivo* rat oral/ip *In vivo* human oral/iv Extent of oral abs >50%	1200–2400 mg/kg (EC 2002)	~2000 mg/kg (EC 2002)	No data	Corrosive (EC 2002)	Severe irritation (EC 2002)	Negative (M & K) (EC 2002)

Table A3.2 Repeated dose, mutagenicity and reproductive toxicity studies for C_4–C_9 alkylphenols

Substance	CAS no.	Repeated dose toxicity (oral dosing)	Mutagenicity	Oestrogenic activity		Reproductive toxicity (oral dosing)
				Receptor affinity*	Uterotrophic activity**	
4-*tert*-Butylphenol (SFT 2007)	98-54-4	Rat 28d study, NOAEL 60 mg/kg/d, gavage (irritation of respiratory tract & increased white cell count) (Japanese Ministry of Health and Welfare 1996) Rat multigeneration study: NOAEL 70 mg/kg/d (decreased body weight gain) (Clubb & Jardine 2006) Limited 20-wk (hamster) & 51-wk (rat) studies: forestomach hyperplasia & papilloma at 600–1230 mg/kg/d, dietary (Hirose *et al*. 1986 & 1988)	*In vitro:* Three Ames, two mouse lymphoma & two mammalian chromosome aberration test *In vivo:* Micronucleus test All negative (Dow 1992; Dean 1985 & Honma 1999)	2.4 X 10^{-6} (Blair *et al*. 2000)		Rat multigeneration study: NOAEL for reproduction 70 mg/kg/d (retarded pup weight in presence of maternal toxicity) (Clubb 2006) Rat 28–39d screening study, gavage: no effects on reproduction at 200 mg/kg/d, the highest dose tested (Japanese Ministry of Health and Welfare 1996)
4-*tert*-Pentylphenol (this report)	80-46-6	Rat development study, NOAEL 50 mg/kg/d, gavage, (clinical signs & decreased body weight gain) (Siglin 1991)	*In vitro:* Three Ames & two mouse lymphoma tests *In vivo:* Micronucleus test All negative	5 X 10^{-6} (Blair *et al*. 2000)	246 % (Yamasaki *et al*. 2002, 2003)	Rat development study, NOAEL for development mg/kg/d, gavage, bent ribs & foetal weight retardation in presence of maternal toxicity (Siglin 1991)
4-*n*-Hexylphenol	2446-69-7	No data	No data	No data	No data	No data
4-*n*-Heptylphenol	1987-50-4	No data	No data	No data	No data	No data
4-Heptylphenol	72624-02-3	No data	*In vitro:* Ames negative (Pharmakon 1993)	No data	No data	No data
4-*tert*-Octylphenol (EA 2005b)	140-66-9	Two 28-d rat studies NOAELs 70 & 150 mg/kg/d, gavage (liver and kidney toxicity) (CIPC 1994 & Huntingdon Research Centre Ltd 1994) Rat multigeneration study NOAEL 15 mg/kg/d, dietary (uterine weight changes) (Tyl 1999)	*In vitro*: Three Ames tests All negative (Hüls 1988b; 1991; Bayer 1982)	1.5 X 10^{-4} (Blair *et al*. 2000)	283% (Yamasaki *et al*. 2002, 2003)	Rat multigeneration study, no effects on fertility; NOAEL for reproduction 15 mg/kg/d, dietary (retarded pup weight in presence of maternal toxicity) (Tyl 1999) Rat development study, NOAEL for development 15.6 mg/kg/d, gavage (post implantation loss in presence of maternal toxicity) (Harazono & Ema 2001)
4-*n*-Octylphenol	1806-26-4	No data	No data	5 X 10^{-5} (Blair *et al*. 2000)	89% (Yamasaki *et al*. 2002, 2003)	No data

Substance	CAS no.	Repeated dose toxicity (oral dosing)	Mutagenicity	Oestrogenic activity		Reproductive toxicity (oral dosing)
				Receptor affinity*	Uterotrophic activity**	
Nonylphenol mixed isomers & 4-nonylphenol (branched) (EC 2002)	84852-15-3 & 25154-52-3	Extensively investigated in rat 28-d, 90-d & multigeneration studies (NTP 1997; Nagao 2001; Latendresse 2004) with a dietary LOAEL of 15 mg/kg/d; NOAEL not identified (kidney toxicity)	*In vitro:* Two Ames & one mammalian gene mutation test *In vivo*: Micronucleus test All negative (EC 2002)	1.9×10^{-4} – 3.7×10^{-4} (Blair *et al.* 2000)	224 % (Yamasaki *et al*. 2002, 2003)	Rat multigeneration studies (NTP 1997; Nagao 2001; Latendresse 2004): no effects on fertility, NOAEL for reproduction 15 mg/kg/d (increased uterine & decreased ovarian weight, accelerated vaginal opening) Rat development study: no effects on development at top dose of 300 mg/kg/d, gavage (Initiative Umweltrelevante Altstoffe 1992)
4-*n*-Nonylphenol	104-40-55	No data	No data	3.2×10^{-5} (Blair *et al*. 2000)	97 % (Yamasaki *et al*. 2002, 2003)	No data

* 17ß-oestradiol =1
** expressed as % of control absolute uterine weight after dosing at 200 mg/kg/d

There is limited evidence from nonylphenol studies that the toxicokinetics of alkylphenols are qualitatively similar in the rat and human. 4-*tert*-Butylphenol is excreted mainly in the urine, with a smaller amount appearing in the bile, but bile is the main route of excretion for nonylphenol, with less material appearing in the urine. The higher degree of biliary excretion for the higher molecular weight alkylphenol is likely to reflect the relationship between the molecular weight and the cut-off for biliary excretion. In summary, the available data suggest that the absorption, distribution and metabolism of the C_4–C_9 alkylphenols are broadly similar. Excretion via the urine appears to be favoured for the lower molecular weight alkylphenols, whereas excretion via the bile appears to be favoured for higher molecular weight alkylphenols.

A3.2.3 Acute toxicity

Several of the alkylphenols, including 4-*tert*-pentylphenol, have been tested in acute oral toxicity studies, and a smaller number have been tested in acute dermal toxicity studies. For the inhalation route only 4-*tert*-butylphenol has been investigated in a guideline study. All of these studies consistently show the alkylphenols to be of relatively low acute toxicity.

A3.2.4 Irritation/corrosivity

The alkylphenols tested in skin or eye irritation studies, including 4-*tert*-pentylphenol, were all found to be irritant or corrosive. Inhalation exposure to 4-*tert*-butylphenol and nonylphenol has been found to cause irritation of the respiratory tract. Thus, the C_4–C_9 alkylphenols have common properties with respect to irritation/corrosivity, probably due to the basic property of the phenol group.

A3.2.5 Skin sensitisation

While some alkylphenols, including 4-*tert*-pentyphenol, gave positive results in maximisation or Bühler skin sensitisation tests, others gave negative results. Within the series of alkylphenols there does not appear to be a relationship between structure and possession of the property of skin sensitisation.

A3.2.6 Repeated dose toxicity

The repeat dose toxicity of the C_4–C_9 alkylphenols has been studied to a limited extent; 4-*tert*-butylphenol, 4-*tert*-pentylphenol, 4-*tert*-octylphenol and nonylphenol have been investigated in repeated dose toxicity or multigeneration studies using oral dosing protocols, and 4-*tert*-pentylphenol has been studied in a repeat dose dermal toxicity study. Several long-term studies are available for 4-*tert*-butylphenol, although these were limited investigations as full ranges of the standard repeated dose parameters were not evaluated. The best-studied alkylphenol is nonylphenol, for which a number of standard repeated dose toxicity and multigeneration studies are available.

In studies with 4-*tert*-butylphenol, 4-*tert*-pentylphenol, 4-*tert*-octylphenol and nonylphenol, decreases in body weight gain and other signs of generalised toxicity were seen after oral dosing at doses in the range 50–500 mg/kg/d. In some studies there was also evidence of mild liver and renal toxicity, shown by increases in organ weight and minor morphological changes. Some studies showed local irritation, and there is some evidence that the oral toxicity of the alkylphenols is enhanced when dosed by gavage, rather than in the diet. Nonylphenol was associated with adverse effects at the lowest dose, although this might be related to the fact that it was also the most comprehensively studied; in a rat dietary multigeneration study histopathological changes in the kidneys (mild tubular degeneration or dilatation) were reported

at 15 mg/kg/d, the lowest nonylphenol dose tested. For 4-*tert*-butylphenol a NOAEL of 70 mg/kg/d was identified, based on a reduction in body weight gain.

In summary, because of limited testing there is little direct information on whether the repeated dose toxicity of alkylphenols varies across the series. From a consideration of their physico-chemical and toxicokinetic properties and findings in other toxicology studies, it can be predicted that repeated dose toxicities will be generally similar across the C_4–C_9 alkylphenol series. This is generally supported by the repeat dose toxicity studies that have been carried out.

A3.2.7 Mutagenicity

4-*tert*-Butylphenol, 4-*tert*-pentylphenol and nonylphenol have been adequately tested both *in vitro* and *in vitro* for mutagenicity. In addition 4-*tert*-octylphenol has been tested *in vitro* for the ability to cause gene mutations. All standard tests were negative.

On the basis of these findings and the lack of structural alerts for genotoxicity, it is predicted that other alkylphenols in the C_4–C_9 series will not be mutagenic.

A3.2.8 Carcinogenicity

The carcinogenic potential of the alkylphenols has not been investigated in standard studies, but on the basis of the essentially negative findings in the mutagenicity tests they are not expected to cause cancer by a genotoxic mechanism. The findings of forestomach hyperplasia and papilloma in two 4-*tert*-butylphenol rodent studies suggest that long-term exposure to high doses of alkylphenols might cause an increase in tumour incidence at the site of contact as a consequence of long-term local irritation.

A3.2.9 Endocrine activity

4-tert-Pentylphenol, 4-*tert*-octylphenol and nonylphenol have been tested *in vivo* for androgenic activity with the Hershberger assay. For all three alkylphenols no evidence of androgenic activity was found. As shown in Table A3.2, alkylphenols have been investigated *in vitro* for binding affinity for the oestrogen receptor. In a comprehensive study of a number of alkylphenols the affinity for the receptor was found to increase as the alkyl chain was lengthened from C_4 to C_9, although it should be noted that the affinity of all were at least three orders of magnitude less than that of 17β-oestradiol. In another study a mixture of 75% 2,4-dinonylphenol and 25% nonylphenol was found to have an affinity more the 10 times less than nonylphenol. Affinity was also influenced by the degree of branching, with straight-chain isomers of octylphenol and nonylphenol being less active than branched-chain isomers. A smaller number of alkylphenols have also been assayed for oestrogenic activity *in vivo* in the uterotrophic assay. This assay also found evidence that oestrogenic potency increases as the degree of branching is increased, but did not show increasing potency with increasing alkyl chain length.

In summary, *in vitro* and *in vivo* screening assays have shown branched chain alkylphenols to lack androgenic activity but possess weak oestrogenic activity. The *in vitro* assay appears to show potency differences not detected by the *in vivo* uterotrophic assay. *In vitro,* the oestrogenic potency of nonylphenol was the highest of the alkylphenols tested.

A3.2.10 Reproductive toxicity

4-*tert*-Butylphenol, 4-*tert*-octylphenol and nonylphenol have been investigated in standard rat multigeneration studies, and prenatal developmental toxicity studies have been carried out in the rat with 4-*tert*-pentylphenol, 4-*tert*-octylphenol and nonylphenol.

None of the three alkylphenols tested in multigeneration studies showed effects on sperm or fertility/mating parameters. The study with 4-*tert*-butylphenol showed effects on ovarian weight, the incidence of vaginal atrophy, the number of implantation sites and litter size at 600 mg/kg/d, the highest dose tested. It is considered that the effects on the number of implantation sites and litter size may be secondary to maternal toxicity, but the mechanism of the effects on ovarian weight and vaginal atrophy is unclear. In lactating pups at 200 mg/kg/d and above body weight gain was retarded and there were delays in reaching developmental milestones. The NOAEL for reproductive effects was 70 mg/kg/d. In the multigeneration study with 4-*tert*-octylphenol, pup body weight gain was decreased and there were delays in developmental milestones at the highest dose tested (150 mg/kg/d). The effects on pup growth and development with 4-*tert*-butylphenol and 4-*tert*-octylphenol are considered to be secondary to maternal toxicity. In two of the three multigeneration studies conducted with nonylphenol there was consistent evidence of oestrogenic effects in females. This was shown by acceleration of vaginal opening in prepubertal animals and, in adults, decreases in ovarian weight and increases in uterine weight. These changes were all seen at 50 mg/kg/d, while one study also reported lengthening of the oestrous cycle at 160 mg/kg/d. There was no convincing evidence of specific effects on prenatal development in the 4-*tert*-pentylphenol, 4-*tert*-octylphenol and nonylphenol developmental toxicity studies.

In summary, the reproductive toxicity of some C_4–C_9 alkylphenols has been studied in multigeneration and developmental studies. 4-*tert*-Butylphenol and 4-*tert*-octylphenol were both associated with retardation of pup growth and development at doses in the region of 150 mg/kg/d; these effects are considered to be secondary to maternal toxicity. The only clear evidence of specific effects on reproductive parameters was seen with nonylphenol, where oestrogenic effects were seen in adult and prepubertal females at 50 mg/kg/d and above. The indication that nonylphenol has a greater potential for oestrogenic effects on reproduction than shorter chain alkylphenols including 4-*tert*-butylphenol and 4-*tert*-octylphenol is supported by evidence from *in vitro* endocrine activity screening assays.

A3.3 Data used to read-across to 4-*tert*-pentylphenol

Toxicokinetics

Of the three C_4–C_9 alkylphenols investigated in toxicokinetics studies, 4-*tert*-butylphenol is closest to 4-*tert*-pentylphenol in terms of structure and physico-chemical properties, although 4-*tert*-octylphenol and nonylphenol have been studied more comprehensively. Consequently, it is proposed that the toxicokinetics data from all three alkylphenols should be used to predict the toxicokinetic behaviour of 4-*tert*-pentylphenol.

Repeated dose toxicity

Regarding studies conducted with 4-*tert*-pentylphenol, repeated dose toxicity received only limited investigation in a developmental study, and a dermal toxicity study provided no information on systemic toxicity. Consequently, the repeated dose toxicity of 4-*tert*-pentylphenol after oral exposure will be predicted using read-across data from other alkylphenols. Of the three C_4–C_9 alkylphenols tested in comprehensive studies involving repeated oral dosing, nonylphenol is the best investigated, with three multigeneration studies and 28- and 90-day studies being available. However, these studies were carried out with mixtures of nonylphenol isomers with variable degrees of branching. On the other hand, 4-*tert*-butylphenol and 4-*tert*-octylphenol exist as single isomers and differ from 4-*tert*-pentylphenol only in the number of carbon atoms in the alkyl chain. Since 4-*tert*-pentylphenol is closer than 4-*tert*-octylphenol to 4-*tert*-butylphenol in terms of structure and physico-chemical properties, it is proposed to use the NOAEL of 70 mg/kg/d obtained in the 4-*tert*-butylphenol multigeneration study to predict the repeat dose toxicity of 4-*tert*-pentylphenol.

Reproductive toxicity

Since 4-*tert*-pentylphenol has been investigated in a prenatal developmental toxicity study but not in a multigeneration study, it is proposed to read-across to other alkylphenols for effects on fertility and postnatal development. As described in the repeat dose toxicity section above, of the three alkylphenols tested in multigeneration studies, 4-*tert*-butylphenol is closest to 4-*tert*-pentylphenol in terms of structure and physico-chemical properties. Hence it is proposed to use the NOAEL of 70 mg/kg/d obtained in the 4-*tert*-butylphenol multigeneration study for these aspects of reproductive toxicity.

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APPENDIX 4

Data collection and peer review process

This report has been produced using publicly available data gathered and assessed by the contractor for the Environment Agency. Additional information, including some original study reports, has been submitted voluntarily by industry.

The Environment Agency has been keen to ensure that the data used in this report are as complete and accurate as possible. Original reports and literature articles for key studies were retrieved and assessed for reliability wherever possible (it is clearly indicated where this was not the case).

The initial data review began in October 2005. The scientific literature was last searched in February 2006 using Web of Knowledge and Cambridge Scientific Abstracts (as well as Google®). The search terms were the CAS number and partial chemical names.

Drafts of this report have been circulated to key stakeholders in UK and European industry for comment (the final opportunity for comment closed in October 2006), as well as members of the UK and international chemical regulatory communities (including the Advisory Committee on Hazardous Substances). All comments received have been addressed in the final report where appropriate. A full list of consultees is included at the end of this Appendix.

In addition, certain technical aspects of the report were peer-reviewed by an independent expert group set up by the Environment Agency for this purpose in September 2006. Again, this report addresses those comments. The experts were:

- Professor Charles Tyler (Exeter University); and
- Dr Susan Jobling (Beyond the Basics Ltd).

Their comments have not been published but are available on request.

LIST OF KEY ORGANISATIONS CONSULTED DURING THE PREPARATION OF THIS REPORT

Industrial organisations

British Association for Chemical Specialities
British Chambers of Commerce
British Chemical Distributors and Traders Association
British Tyre Manufacturers' Association Ltd
Bureau de Liaison des Industries du Caoutchouc (BLIC) (European Association of the Rubber Industry)
Chemical Industries Association
Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques (CESIO)
Conseil Européen des Phénols Alkylés et Derivés (CEPAD)
European Phenolic Resins Association
European Polymer Dispersion and Latex Association
International Institute of Synthetic Rubber Producers
PCC Synteza S.A.

SASOL Germany GmbH
Schenectady International Inc.
Technical Committee of Petroleum Additive Manufacturers in Europe ('Additives Technical Committee')

UK government bodies

Advisory Committee for Hazardous Substances
Department for Environment, Food and Rural Affairs (Defra)
Department of the Environment, Northern Ireland
Department of Health
Department of Trade and Industry
Food Standards Agency
Health and Safety Executive
Health Protection Agency
Natural England
Pesticides Safety Directorate
Scottish Environment Protection Agency
Scottish National Assembly
Veterinary Medicines Directorate
Welsh Assembly

European regulatory authorities

European Union Technical Committee for New and Existing Substances

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