European Union Risk Assessment Report

P-TERT-BUTYLPHENOL

CAS No: 98-54-4

EINECS No: 202-679-0

RISK ASSESSMENT

FINAL APPROVED VERSION

LEGAL NOTICE

Cataloguing data can be found at the end of this publication

Luxembourg: Office for Official Publications of the European Communities, [ECB: year]
ISBN [ECB: insert number here]

Printed in Italy

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RISK ASSESSMENT

Final report 2008

Norway

The rapporteur for the risk assessment report on p-tert-butylphenol is the Norwegian Pollution Control Authority in consultation with the Directorate of Labour Inspection, on behalf of the European Union. The scientific work on this report has been prepared by the National Institute of Public Health, the Norwegian Institute of Water Research and the National Institute of Occupational Health.

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Date of Last Literature Search : 2004
Review of report by MS Technical Experts finalised: 2008
Final report: 2008

The last full literature survey was carried out in 2002 for HH and in 2004 for ENV. Targeted searches have been carried out subsequently for example on micronucleus test, endocrine effects. Toxicity data have been added until 2006 and exposure data until 2007 for consumers.

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

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

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT[4]

CAS Number: 98-54-4
EINECS Number: 202-679-0
IUPAC Name: Phenol, 4-(1,1-dimethylethyl)

Environment

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to endocrine disruption. Based on *in vitro* data on ptBP and read across from similar alkyl phenol compounds, including p-tert-pentylphenol, which have shown endocrine disrupting properties *in vivo*, it is concluded that further testing should be required for ptBP. As a "Tier 2 test" an Extended Early Life-Stage test on fish according to the draft OECD guideline will be performed.

Conclusion (i) applies to phenolic resin production site 5, where the PEC_{marine} as well as the PEC_{STP} have been calculated using generic parameters and a risk to the marine environment and to microorganisms in the WWTP has been identified. The exact values for the PEC/PNEC ratios are not given as the tonnage used at this site is considered confidential. Further exposure information is needed in order to refine the the PEC_{marine} and the PEC_{STP} for this site.

Conclusion (i) applies to phenolic resin production site 6 where no site specific data is available. No $PEC_{aquatic}$ and no PEC_{STP} could be derived and therefore no risk assessment for the aquatic compartment and for microorganisms in the WWTP has been carried out. Further exposure information is needed in order to calculate a $PEC_{aquatic}$ and a PEC_{STP} for this site.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to the life-cycle steps production, to the production of phenolic resins, where site specific data are available, for the generic sub-scenario 2 and 3 of the production of epoxy resins and to the production of polycarbonate resins for all environmental compartments.

Conclusion (ii) applies to phenolic resin production site 8 for the marine environment. The PEC/PNEC ratio for the marine environment is below 0.03.

4 Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

According to information from industry no emissions to the environment are expected from the use of ptBP in the production of oilfield chemicals and the scenario "Hydrogenation" and therefore conclusion (ii) applies.

No risk assessment for secondary poisoning has been performed. Available data indicate that ptBP is unlikely to bioaccumulatein the food chain. No further information is considered necessary.

Conclusions ii) for the aquatic and the terrestrial compartment have to be seen as provisional until possible endocrine effects in fish have been resolved.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the generic scenario for phenolic resin production and to the generic sub-scenarios 1 and 4 of the epoxy resin production for the aquatic compartment (including sediment). The PEC/PNEC ratios for phenolic resin production and for sub-scenarios 1 and 4 of the epoxy resin production are 28, 121 and 30, respectively.

Conclusion (iii) also applies to the generic scenario for phenolic resin production and to the generic sub-scenarios 1 and 4 of the epoxy resin production for the terrestrial compartment (PEC/PNEC ratios 15, 66 and 17, respectively) and for microorganisms in WWTPs (PEC/PNEC ratios 1.2, 5.2 and 1.3, respectively).

For production of phenolic resins site specific information has been obtained only for about 50 % of the total tonnage used in this use category. Therefore a generic scenario has been conducted which resulted in a risk to the aquatic and the terrestrial compartment, as well as to microorganisms in WWTPs. The exposure assessment for the production of phenolic resins is based on an average emission factor obtained from the site having the highest emissions participating in the EPRA water monitoring program and on default parameters from the TGD. The size of the site has been chosen in close cooperation with industry.

Concerning the production of epoxy resins no site specific data has been obtained by industry but only qualitative descriptions of the processes involved. No site-specific data on emissions to the environment has been obtained. The information received resulted in four sub-scenarios, which have been proposed by industry. TGD default parameters have been used to calculate environmental concentrations. The TGD values have partly been adapted due to information from industry (sub-scenario 4).

Regarding the release from ambient cured epoxy products no further information on releases to the enviromment has become available.

More site specific information may give evidence of lower emissions than estimated in the generic scenarios of the use categories "phenolic resins" and "epoxy resins", maybe resulting in no risk. However, no such data could be made available despite of much effort that has been undertaken by the ptBP producers to obtain this information during the last 1 ½ years.

Human health

Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to the endpoints acute toxicity, irritation, sensitisation, mutagenicity and carcinogenicity for all scenarios.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the endpoints of repeated dose toxicity and reproductive toxicity after dermal exposure arising from formulation and processing (production of epoxy resins) and after inhalation and dermal exposure arising from end use of phenolic resins and end use of epoxy resins. Conclusion (ii) is reached for all other endpoints and scenarios.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios and endpoints for consumers.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios and endpoints for humans exposed via the environment.

Combined exposure

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios and endpoints for combined exposure. Combined expsure is described as exposure to humans as consumers and via the environment. For humans exposed both in the working environment as well as consumers or indirect via the environment, the occupational exposure will exceed the other exposure sources by far, so it has not been considered relevant to assess combined exposure including workers.

Human health (physico-chemical properties)

PtBP has low vapour pressure. No data is available for flammability. The substance is reported to be combustible. The flash point is about 115°C. The chemical structure of this compound does not suggest a likelihood of explosivity or oxidizing properties. The risks from physicochemical properties are of no concern to either subpopulation (workers, consumers or humans exposed via the environment).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios

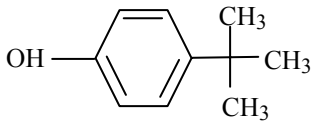
CONTENTS

Content of tables:

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 98-54-4
EINECS Number: 202-679-0
IUPAC Name: 4-(1,1-Dimethylethyl)phenol
Molecular formula: C10H14O
Structural formula:



Molecular weight: 150.22 g/mol
Synonyms: 4-tert-Butylphenol
p-tert-Butylphenol
Phenol, 4-(1,1-dimethylethyl)
Butylphen

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: ≥96 % (w/w) (SASOL, Germany GmbH).

Formation of 2,4,6-tri-tert-butylphenol during the production of p-tert-butylphenol theoretically is possible and can not be fully excluded. However, the material is not detected in the final product. The detection limit for 2,4,6-tri-tert-butylphenol in the final product (ptert-butylphenol) is below 2 ppm. The situation for 2,4-di-tert-butylphenol is similar.

1.3 PHYSICO-CHEMICAL PROPERTIES

Water solubility

The following values are available. The value of 610 mg/l was obtained experimentally during a test following OECD guideline 105 (at 25 °C):

500 mg/l (Huels AG, Marl)

700 mg/l (Norbas and Envichem database)

610 mg/l (MITI, 1997)

800 mg/l (Böddeker & Bengtson, 1990)

429 mg/l QSAR (EPIsuite v3.1)

As the value of **610 mg/l** was obtained from an OECD guideline test, this value is used in the RAR.

Partition coefficient octanol/water

The following data are available with respect to the partition coefficient octanol/water:

Log octanol/water coefficient

2.44 (method: Flask shaking, Huels AG, Marl)

3.31 (method: Flask shaking, Huels AG, Marl)

3.29 (method: OECD 107, MITI, 1997)

3.42 QSAR (Epiwinsuite v3.1)

The log Kow of 3.29 was obtained from an OECD guideline test, which has been performed according to GLP and this value will be used in the RAR.The good agreement between the QSAR estimated value and the measured Log Kow value of **3.29** indicates this value to be the most representative value for 4-tert-Butylphenol.

Vapour Pressure

IUCLID records a value of 0.5 Pa at 20 ^{o}C (Huels AG Marl), 18 Pa at 50 ^{o}C and 1300 Pa at 115 ^{o}C; however, no information regarding the method has been submitted. In EPI suite (3.1) an experimental value of 0.0381 mm Hg (=5.1 Pa) at 25 ^{o}C with reference Chao, J. et al (1983) is available. The EPI suite QSAR value is estimated using 3 different methods and are in the range 0.0045-0.017 mm Hg (0.6-2.3 Pa) at 25 ^{o}C. Interpolation of the Huls AG data gives a vapour pressure of 3.5 Pa at 25 ^{o}C. Therefore it seems to be a fairly good agreement between different methods and the data of Huels AG are used in the risk assessment. A vapour pressure of 0.5 Pa at 20 ^{o}C is used in this risk assessment.

Other physical- chemical properties

The Henry's law constant is calculated from the vapour pressure, molecular weight and water solubility of the substance using the following equation:

$$\text{Henry's Law Constant} = \frac{\text{Vapour Pressure (Pa)} \times \text{Molecular Weight (g/mol)}}{\text{Water Solubility (mg/l)}}$$

Using a vapour pressure of 0.5 Pa, a molecular weight of 150.22 g/mol and a water solubility of 610 mg/l gives a Henry's law constant for ptBP of 0.123 Pa.m^{3}.mol^{-1}.

PtBP may act as a weak acid and has a pKa value of 10.16 at 25 ^{o}C (MITI, 1997). However, under environmentally relevant conditions ptBP is predominantly present as the non-dissociated molecule. At pH 7 only 0.07% of the substance is ionised and 0.7 % at pH 8.

Table 1-1: Summary of physico-chemical properties

Property	Value	Reference and comments
Physical state	White flakes	At 20° C
Melting point	Ca 100°C	Huels AG, Marl
Boiling point	237.5° C	At 1,013 hPa, Huels AG, Marl
Relative density	0.92 g/cm3	At 110 ° C, Huels AG, Marl
Vapour pressure	0.5 Pa	At 20° C, Huels AG, Marl
Water solubility	610 mg/l	At 20° C (mean value)
Partition coefficient n-octanol/water (log value)	3.29	MITI 1997 (OECD 107)
pKa	10.16	At 25°C MITI, 1997 (OECD 112)
Granulometry	-	
Conversion factors	-	
Flash point	About 115° C	Huels AG, Marl
Autoflammability	510° C	Huels AG, Marl (DIN51794)
Flammability	-	
Explosive properties	-	
Oxidizing properties	-	
Viscosity	2.4 mPa s	At 110° C Huels AG, Marl

1.4 CLASSIFICATION

P-tert-butylphenol is not classified according to Annex I

1.4.1 Current classification

Producers currently classify /label the material as:

Human Health: Xi, R36/37/38

Environment: N, R51/53

1.4.2 Proposed classification

The Technical Committee on Classification and Labelling (TC C&L) in EU have agreed to classify ptBP as follows but it was not included in Annex I of Directive 67/548/EEC since the classification was agreed in the TC C&L group after the closure of the 31. ATP to the 67/548/EEC directive. It will be included in an ATP to the CLP regulation.

Repr. Cat. 3; R62[5]

[5] Commission Working Group on the Classification and Labelling of Dangerous Substances Meeting on Health Effects of Existing Chemicals, Pesticides & New Chemicals September 26-28, 2007

Xi; R37/38-41 [6],
N; R51-53 [7],

Symbol: Xn harmful
N dangerous for the environment

Risk phrases:

R 51-53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
R 37/38: Irritating to respiratory system and skin
R 41: Risk of serious damage to eyes
R 62: Possible risk of impaired fertility

Safety phrases:

S 2: Keep out of the reach of children.
S 26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S 36/37/39: Wear suitable protective clothing, gloves and eye/face protection.
S 46: If swallowed, seek medical advice immediately and show this container or label.
S 61: Avoid release to the environment. Refer to special instructions/Safety data sheets.

[6] Commission Working Group on the Classification and Labelling of Dangerous Substances Meeting on Health Effects of Existing Chemicals, Pesticides & New Chemicals March 21-24, 2006
[7] Commission Working Group on the Classification and Labelling of Dangerous Substances Meeting on Environmental Effects of Existing Chemicals, Pesticides & New Chemicals September 28-30, 2005

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

For the assessment of production volumes, breakdown of uses and applications of ptBP, as well as for the assessment of occupational and environmental exposure a questionnaire was developed and sent to producers and major users/user associations in 2001. The European Phenolic Resins Association (EPRA) conducted an Alkylphenol Water Monitoring Study in 2005/2006 in order to determine emissions of ptBP from phenolic resin production sites to the aquatic environment.

Separate questionnaires have been filled in by producers/users for different sites. Filled-in questionnaires were sent back from all three producers,one of them using ptBP almost exclusively captive on site. All three polycarbonate producers have sent site specific information, but for the used category epoxy resins production the number of sites is unknown and exposure information is missing. With regard to phenolic resin production sites a number of 20-25 processing sites is assumed to be realistic in 2005. Exposure information is available for a total of 9 phenolic resin production sites (combined 2001 and 2005 situation); but for about 14 sites information is missing, see chapter 3.1.2.3. For the use category hydrogenation one major producer out of four responded with site specific information. The results of the questionnaires are treated confidentially. Production figures have been collected by CEPAD – EBPP (European Butyl Phenol Panel), a Sector Group of CEFIC and EPRA.

PtBP is produced in a controlled closed system. Production of derivatives is also performed in controlled closed systems, although the processes itself may differ.

Waste waters (if any) are normally directed to industrial wastewater treatment plants on site or incinerated. Sludges from WWTP, if any, are normally incinerated.

In Europe 3 producers produced ptBP in 2001. Production sites are located in Germany, France and Switzerland. Although Switzerland is not a member of the EU, the production site in Switzerland is included for the risk assessment (production volumes are treated as EU production, “import” figures only relate to import from overseas). One producer is almost exclusively using ptBP captive on site (about 95%), the rest being sold to one single customer.

The production process used by all producers is the same and is described below in more detail:

Phenol and isobutene are reacted in the presence of a fixed bed ion exchange resin in either a continuous process (2 producers) or a batch process (one producer). Following reaction the product is distillated to eliminate unreacted starting materials (these are directed back to the reactor). In a distillation step the final product is separated. The pure product is stored as a molten product at 130 °C under a nitrogen blanket and shipped in trucks. Due to the storage conditions releases to the atmosphere during storage are completely excluded. Another part of the molten product is processed to flakes in a strictly closed system. The flakes are automatically filled into 25 kg or “big bags” (about 400-800 kg).

The by-products of the second distillation step are separated and either used for production of other materials or incinerated in the on-site incineration plant.

Within the whole process wastewater is only produced at one site, which is treated in a WWTP. The system is strictly controlled and closed. To avoid a discolouration of the ptBP nitrogen blankets are always used.

2.1.2 Production capacity

Data in this section are based upon a survey of ptBP producers and users (CEPAD, 2002).

Three companies produced ptBP in 2001 within the EU. One of the producers used ptBP almost exclusively captive on site. The lifecycle of ptBP is shown in Figure 1. From 2004 there are only two producers. In consultation with industry it had been agreed to maintain the 2001 figures in the RAR for confidentiality reasons. Moreover, no updated figures for the 2004 situation have been provided and therefore the data from 2001 are used.

Table 2-1: Production volume, exports and imports (2001)

	Amount (tonnes/year)
Production volume in EU	25,251
Exports from EU	734
Imports into EU	2,100
Captive use	Confidential
Tonnage (Use in EU) (Production volume + Imports of ptBP – Exports of ptBP)	26,617

2.2 USES

2.2.1 Introduction

By far the major use is the use as a monomer in chemical synthesis, e.g. for the production of polycarbonates, phenolic resins, epoxy resins etc. The material is also hydrogenated to the corresponding cyclic alcohol. Very minor amounts are used for the production of oilfield chemicals (in principle covered by phenolic resins production). Previously ptBP was used as an intermediate for the production of an active ingredient in agrochemicals. Previously also a very small amount of ptBP was marketed for the use as an anti-skinning agent in decorative paints; the concentration of ptBP in the decorative paint was reported to be < 0.1 %. These uses are no longer relevant according to information from industry.

According to information from the Norwegian Product Register ptBP was registered in 207 products with a total amount of ptBP of 3.8 tons in 2003 (see Table 2-2). In 2005 111 products with a total amount of ptBP of 2.97 tons were registered.

Table 2-2: Information on ptBP containing products form the Norwegian Product Register (2003)

Weight % [1]	Number of products	Corresponding amount of ptBP max (tons)
0-1 %	169	0.698
1-5 %	13	0.811
5-10 %	16	1.735
10-100 %	9	0.558

[1] Industry has commented that the concentration of ptBP stated for the final product in this column does not relate to free, but chemically bound ptBP. It should be noted that this survey also identifies chemicals intended for use in processing or formulation as "products"

The Nordic SPIN-database (www.spin2000.net) provides more details on the use of ptBP in the Nordic countries. Table 2-3 lists the tonnages for the different countries.

Table 2-3: Data regarding ptBP from SPIN database

	1999	2000	2001	2002	2003	2004
DK		54.7	36.7	30.8	20.7	24.2
FIN			29.1	5.2	13.9	8.1
N		15.5	6.4	3.7	3.1	3.2
S	13.0	13.0	7.0	5.0	6.0	5.0

Table 2-4 shows examples of product types with corresponding concentration of ptBP and the amount of ptBP in the product types. Because of confidentiality reasons only product types with more than 3 products are shown, the total amount of ptBP is therefore different from Table 2-2. Consumer uses have been identified for adhesives and paint and varnishes. For further discussion see chapter 4.1.1.3.1.

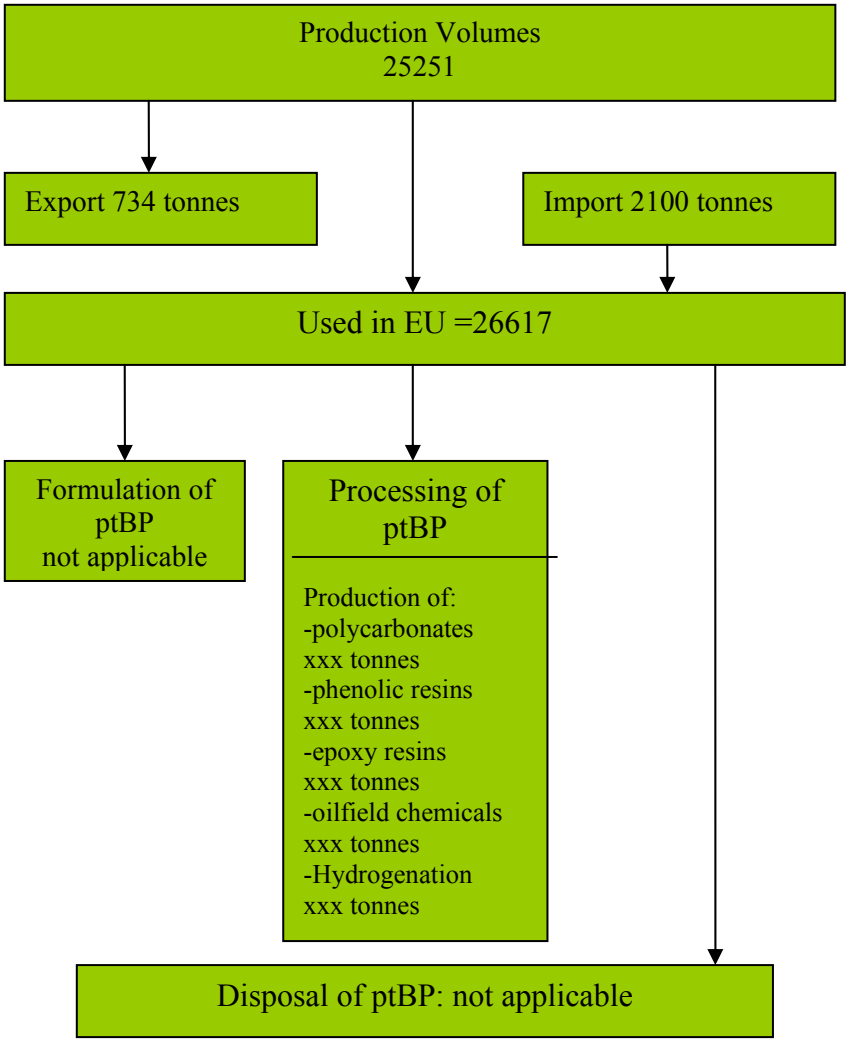
Table 2-4: Chemical products containing ptBP on the Norwegian Market 2003

Product type	Concentration in product (%) [1]	corresponding amount of ptBP max (tons)	Consumer identified
Binding agents	0-10	0.008	
Colouring agents	0-1	0.000	
Impregnation/proofing-chemicals protecting from damp, fungus etc	0-1	0.002	
Adhesives	0-1 1-10	0.025 0.438	X X
Paint and varnish, volatile organic thinner, active corrosion inhibitor	0-1 1-60	0.004 0.097	X
Paint and varnish, volatile organic thinner, decorative /protection	0-1 1-5	0.416 0.072	X
Hardeners to paint and varnish	0-5 5-10 10-60	0.191 0.239 0.067	
Filling agent	0-5	0.001	X

[1] Industry has commented that the concentration stated for the final product in this column does not relate to free, but chemically bound ptBP.

An estimation of the breakdown application/uses was submitted and is considered confidential.

Figure 1: p-tert-Butyphenol lifecycle (volumes represent 2001 figures)



XXX: Data are confidential. Only 2 producers sold the product to the market, the 3rd producer used the material captive on site.

In the polymers ptBP is chemically bound in the matrix (covalent binding). The residual concentrations of ptBP in the polymers (e. g. polycarbonates, phenolic resins etc.) are limited (e. g. < 5ppm in polycarbonate and approximately 3% in phenolic resins). Since the polymers are further processed to finished products, the concentration of free residual monomers in the final products is much lower.

Table 2-5: Summary of relevant industry categories and use categories

Product category	Industry category	Use category
Polycarbonates	IC11	UC43
Phenolic resins	IC11	UC43
Epoxy resins	IC 3	UC33
	IC11	UC43
Oilfield chemicals	IC3	UC33
Hydrogenation	IC3	UC33

2.2.2 Scenarios

2.2.2.1 Use of ptBP as chain terminator for polycarbonate synthesis

P-tert-butylphenol is used by 2 companies in Europe for the production of polycarbonates (3 production sites). Remaining polycarbonate producers do not use ptBP as a chain-terminating agent. Detailed information regarding volumes and emissions, as well as a description of the process is available for all three sites.
P-tert-butylphenol is used as a chain terminator in the synthesis of polycarbonate polymers. Polycarbonate resins produced with p-tert-butylphenol contain 1-3 wt % of p-tert-butylphenol, reacted and bound into the polymer chain.

2.2.2.1.1 Description of the production process

Most polycarbonate is produced in fully contained, closed systems by an interfacial polymerisation process utilising phosgene and bisphenol-A as starting materials. To adjust the molecular weight of the polymer, a chain-terminating agent like p-tert-butylphenol is used.

The process involves stirring bisphenol-A and the chain-terminating agent in a mixture of methylene chloride and water, while adding phosgene in the presence of a catalyst. Sodium hydroxide solution is added to maintain the correct reaction pH. The by-product of the reaction is sodium chloride, which concentrates in the aqueous phase. The polymer dissolves into the methylene chloride phase. Phosgene addition continues until all the phenolic groups are converted to carbonate functionalities. Some hydrolysis of phosgene to sodium carbonate may also occur. When the reaction is complete, the methylene chloride solution of polymer is washed first with acid to remove residual base and amine, then with water. The aqueous sodium chloride stream can be reclaimed, ultimately regenerating phosgene. There are many variations to this process, including the use of many different types of catalysts, continuous or semi-continuous processes and methods that rely on formation of bischloroformate oligomers by polycondensation.

Methods for the isolation of the polymer product include anti-solvent precipitation, removal of the solvent in boiling water, spray drying and melt de-volatilisation using a film evaporator. The polymer is isolated as strictly dry granules, prills or flakes.

2.2.2.1.2 Applications of polycarbonate

The main uses of polycarbonate are the following:

- Compact discs, DVD, and CD Rom manufacture
- Solid and multi-wall sheet in glazing applications and films
- As polycarbonate blends for diverse injection moulded functional parts used mainly in the electrical and electronics industry and the automotive industry
- Containers for storage of food and beverages, tableware.

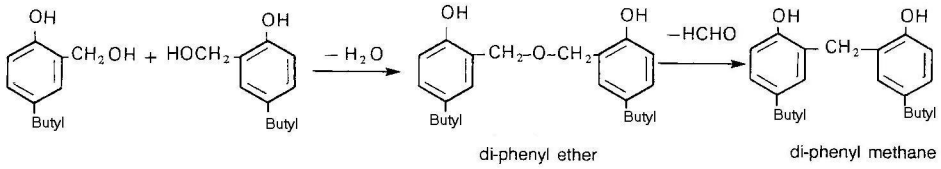
2.2.2.1.3 Residuals of p-tert-butylphenol in polycarbonate resins

The residual concentrations of non-reacted p-tert-butylphenol in polycarbonate have been measured. The concentration was found to be non detectable, at a limit of detection of 5 ppm.

2.2.2.2 Use of ptBP in phenol/formaldehyde resins

Detailed information regarding the use of ptBP in the phenol/formaldehyde resins production is available for several major resin producers in Europe. Information covers about 50 % of the total ptBP volume used in this application.

Butylphenol is used in phenol/formaldehyde resins, either alone or mixed with other phenols. The reaction between p-tertiary-butylphenol and formaldehyde can be simplified into three stages. The reaction conditions and reactant ratios will determine how far the reaction progresses.



Phenolic resins, including p-tertiary-butylphenol resins, are of two main types:

Novolacs, which are thermoplastic, are made with a molecular excess of phenol over formaldehyde and usually catalysed with acid (for example hydrochloric, sulphuric or oxalic acid)

Resoles, which are heat reactive, are made with a molecular excess of formaldehyde over phenol and are usually catalysed with alkali (for example sodium hydroxide, ammonia, amines).

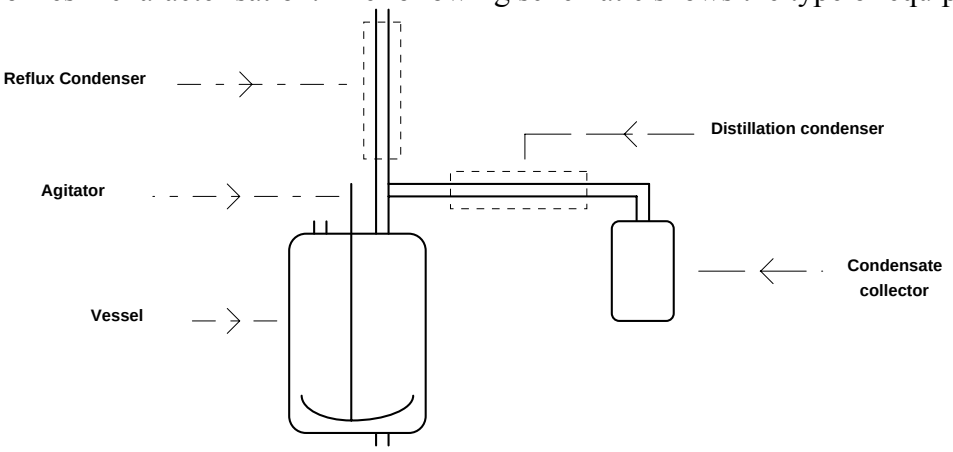
2.2.2.2.1 Manufacturing methods - The basic process and equipment requirements

The phenol/formaldehyde resins manufacture is based almost exclusively on a discontinuous batch processes although continuous processing may be applied for the later stages of

production of ptBP/formaldehyde resins. The batch process uses a traditional reactor or 'kettle', which has the following elements:

Means of heating and cooling
Means of agitation
Means of charge and discharge

In addition to these basic parameters, the ability to apply vacuum to the vessel is often important to allow for the controlled reflux and distillation of some formulations. Condensate from distillation is drained off to a secondary collection vessel. The value of vacuum in both of these processes is that the temperature of vaporisation can be controlled, thereby allowing accurate maintenance of temperature profile during the reaction. This is often a critical aspect of resin characterisation. The following schematic shows the type of equipment used:



Depending on the formulation, the process and the heat stability of the resin, the reactor size can vary from 1 to 40 m^3.

Methods of manufacture

Reactor loading
P-tertiary butylphenol is normally introduced into the reactor as a molten liquid from storage tanks via a closed system. It may also be loaded as a solid from bags, in which case dust extraction will be necessary to protect workers from exposure.

There are essentially two main approaches in common use. These are:

'En-masse' or 'Batch' process
As its name suggests, the 'en-masse' approach involves the addition of the total requirement of main reactants necessary to complete the reaction at the outset. The reaction is initiated by the addition of the catalyst and the subsequent application of heat.

'Continuous addition' or 'Semi-batch' processes
The continuous addition or semi-batch process involves the controlled addition of one of the raw materials during the reaction phase. Most typically, the reactant introduced gradually is formaldehyde, since it is usually present in solution.

In some cases a combination of both processes may be employed. The reaction may also be conducted in solution in (e.g.) xylene.

In typical (but not necessarily all) processes the reaction of ptBP with formaldehyde will be conducted under reflux conditions either until all the formaldehyde has reacted or to a predetermined end point. The resultant salts may then be neutralised and removed by washing with water and then the resin distilled to remove remaining water and, in the case of resoles, to continue the reaction until the required molecular weight is achieved. This stage may be a batch process or a continuous process.

The final resin will be discharged:

- as a solution in an organic solvent, for example, xylene - the solution will be transferred into drums, IBCs or tanks or
- as a molten solid into a cooled tray -the solidified resin will be broken up and packaged or
- as flakes or pastilles on to a cooled belt - these will be packed into (e.g.) bags or FIBCs or
- as an aqueous dispersion, packed into drums, IBCs or tanks.

2.2.2.2.2 Use Patterns

Butylphenol/formaldehyde resoles are used as intermediates in contact and pressure sensitive adhesives, coatings, printing inks and electrical varnishes. Novolaks are used in rubber compounding (tyre manufacture) and are ethoxylated for use in oil recovery.

Adhesives:
Butylphenol/formaldehyde resins are used to improve temperature and solvent resistance, tack and adhesion of polychloroprene rubber based adhesives. The resin is pre-reacted with a metal oxide (typically MgO) then blended with the rubber. Further reaction takes place when the adhesive is applied and the solvent evaporates. Dispersions or emulsions of ptBP/formaldehyde resins can be used with rubber lattices to produce water-based adhesives.

Coatings:
Butylphenol/formaldehyde resins are used in coatings in combination with other resins (such as epoxy, alkyd, or natural resins, maleinised oils or polyvinylbutyral). Principal applications are automotive coatings, metal containers (typically epoxy/butylphenolic) and marine paints. All these involve reaction of the ptBP/formaldehyde resin with the other components.

Printing Inks:
Butylphenol/formaldehyde resins are reacted with rosin for use primarily in gravure and off-set inks for magazine publishing. They release solvent completely and rapidly and are therefore ideally suited to the high speed processes employed.

Electrical Varnishes:
PtBP/formaldehyde resins are used together with alkyd resins in varnishes for secondary insulation of electrical components. This includes impregnation of windings in motors and transformers and coating of core plate laminates.

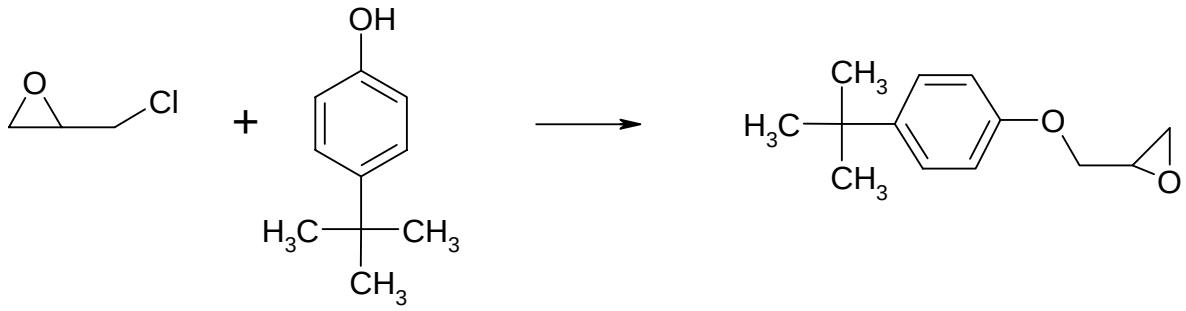
Rubber Compounding:
Butylphenol/formaldehyde resins are used to improve the tack of compounded rubber in order to ensure the layer to layer adhesion of tyres during vulcanisation. Residual ptBP concentrations far below 0.1% have been measured.

2.2.2.3 Use of ptBP in the epoxy industry

Four different uses of ptBP in the epoxy industry have been identified:

1. Starting material in the manufacturing of ptBP glycidylether (ptBP-GE) used as reactive diluent / thinner in epoxy resin systems“

Low molecular weight glycidyl ethers (GE) are used to reduce the viscosity of epoxy resin systems. For the production of ptBP glycidylether the ptBP is reacted with an excess of epichlorohydrine (under alkaline conditions). Following the reaction the excess of epichlorohydrine is removed by distillation. The glycidyl ether normally contains about 5 – 10 % of unreacted ptBP. The ptBP-GE is used in concentrations of about 10 – 30 % in the final epoxy resin system to reduce the viscosity. A recent input received from a producer of ptBP-GE shows that levels of unreacted ptBP in GE are in the range of 0.1-0.3 %, thus far below the estimate of 5-10 %.



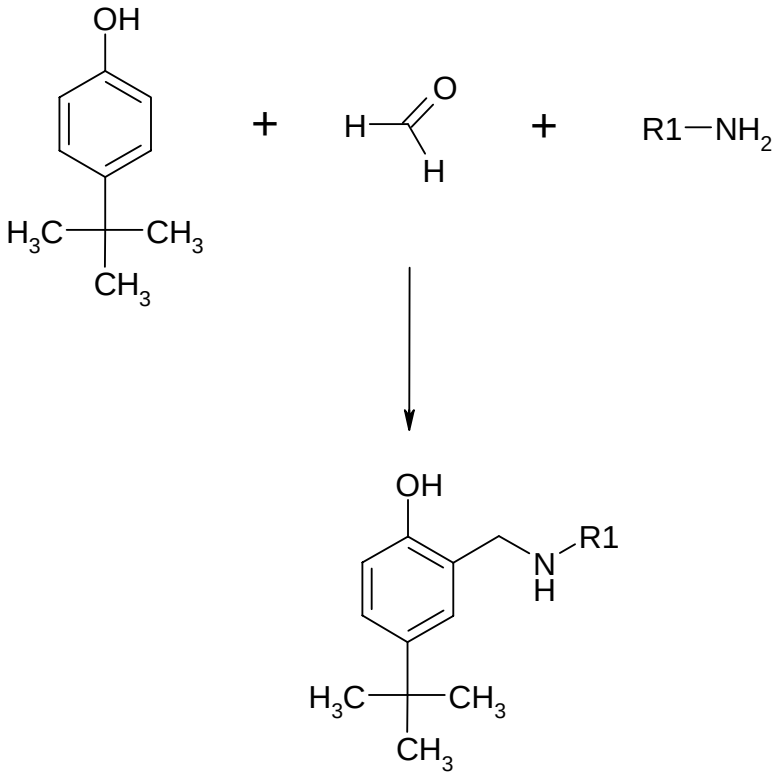
2. Use as an accelerator in hardening agents for epoxy resins based on amines

For the production of the hardening agent ptBP is added to the amine component (about 5 – 20%) and solved by warming. The amine salt is added to the epoxy resins in concentrations of 30 – 50 %. Following the hardening process the concentration of residual ptBP is in the range of 4.6 – 6.7 %. The Association of Plastic Manufacturers in Europe (APME) has commented that “the statement that cured systems still contain 4.6-6.7 % unreacted ptBP seems to be very high, but we have no data”.

If used as an accelerator in the hardening process without heating residual ptBP is not chemically/covalently bound in the matrix but closely bound in the matrix. The matrix itself is completely insoluble in water.

3. Starting material in the production of "Mannich bases" used as hardening agents for epoxy resins

"Mannich" bases are used as hardening agents (for a fast hardening process) in the epoxy resins industry. For the production of the "Mannich bases" ptBP is reacted with the amine component and formaldehyde. Following the reaction process the water that was formed during the reaction is removed via distillation using a vacuum. The final reagent may contain unreacted ptBP (up to 30 %) as well as amine.



Using a blend of about 100:40 or 100:50 (epoxy resin:"Mannich reagent") the concentration of residual ptBP in the final epoxy resin is in the range of 8.6 – 10 %. The Association of Plastic Manufacturers in Europe (APME) has commented that "the level of 8.6-10% free ptBP in the cured systems seems to be very high, but we have no data".

Residual ptBP is not chemically/covalently bound in the matrix but closely bound in the matrix. The matrix itself is completely insoluble in water.

4. Modifier/chain terminator in the manufacturing of epoxy resins

PtBP is used to a limited extent as chain modifier in the manufacturing of certain epoxy resins. PtBP modified epoxy resins are used as polymeric binder in industrial corrosion protective coatings (ambient cured epoxy coatings, epoxy powder coatings, heat cured coatings). In this application, the ptBP is fully reacted to the epoxy backbone and residual levels of unreacted ptBP in the epoxy resin are extremely low (typically in the ppm range). One company reported about a historical use of a ptBP modified epoxy resin in a lining for sanitary cans. The resin was modified with 0.75 % of ptBP and contained up to 250 ppm of unreacted ptBP. Migration levels into food simulants were found to be below the SCF

(Scientific Committee for Food) migration limit of 50 ppb. The manufacturing of this grade was terminated in mid 90's.

2.2.2.4 Hydrogenation (production of p-tert.-butylcyclohexanol)

PtBP can be hydrogenated to yield the respective alcohol, i.e. p-tert.-butylcyclohexanol. Emissions of ptBP can only occur during the hydrogenation process, but not during the use of the alcohol. The hydrogenation is done in a strictly controlled closed system under high pressure using hydrogen (highly explosive).

2.2.2.5 Production of Oilfield Chemicals

Butylphenol/formaldehyde resins are ethoxylated to produce specialised surfactants for the separation of crude oil in aqueous refinery effluent from off-shore oil. These products greatly reduce the amount of crude oil discharged to the environment.
In all these processes the resin is mixed with other resins/components and, with the exception of tyre tackifiers, further reaction takes place. This reaction will also occur with any free p-t-butylphenol in the resin. While it is common for commercial ptBP/formaldehyde resins to contain up to 3% free p-t-butylphenol, this dilution and reaction will reduce the free monomer to very low levels.

2.3 TRENDS

Figure 2 shows the amount of ptBP in products registered yearly by the Norwegian Product register. From 1992 until 1998 the amount of ptBP in products increased from 10 tons up to 29 tons in 60 products, while from 1999 a decline down to about 4 tons in ca 200 products was observed in 2001. From 2001 to 2005 the amount of ptBP registered by the Norwegian Product Register is more or less constant. In the other Nordic countries a decline could be observed from 2000 until 2004 as well (see Table 2-3). However, there is no information available indicating that this trend is also representative for Europe.

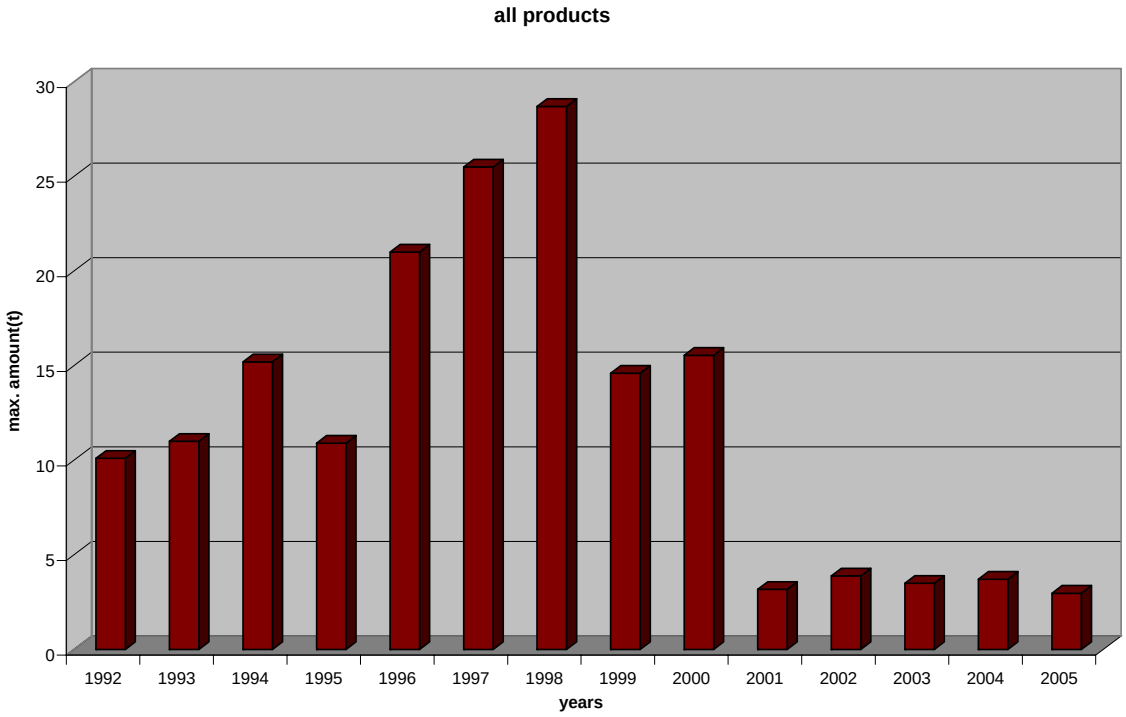


Figure 2: Amount of ptBP in products registered in Norway 1992-2005

2.4 LEGISLATIVE CONTROLS

Commission Directive 2002/72/EC of 6 August 2002 relating to plastic materials and articles intended to come into contact with foodstuffs.
PtBP is on the "positive" list in Annex II "List of monomers and other starting substances which may be used in the manufacture of plastic materials and articles", Section A, with a legally binding specific migration limit (SML) of 0.05 mg/kg (50 ppb).

SML = Specific migration limit in food or food simulant, unless it is specified otherwise.

Chemical Agents Directive (98/24/EEC)

No occupational exposure limit value (OEL) have been established for ptBP at Community level, but a few Member States have established national limits values of (0.5 mg/m^3) 8 hour time weighted average.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

In considering releases of ptBP to the environment the life cycles of the major products of ptBP have to be considered. PtBP is used as a chemical intermediate for the production of resins and polycarbonates and is hydrogenated to the respective alcohol. Life cycles with potential release to the environment are the production of ptBP itself, processing (i.e. production of resins, polycarbonates, oilfield chemicals, agrochemicals and hydrogenation to alcohol) as well as potential releases of residual ptBP from the processed goods (e.g. resins, polycarbonates) or finished products.

Releases of ptBP during the use of the finished products are generally low or negligible. For example polycarbonates have a residual level of free ptBP of <5 ppm. However, as described in chapter 2 (see chapter 2.2.2.3) cured epoxy systems may still contain significant amounts of unreacted ptBP (up to 5-10 %). In general, high temperature cured epoxy formulations are not expected to release significant quantities because of low residual amounts of free ptBP. This applies especially for can coatings, where food approval requirements have to be fulfilled. However, it is state-of-the-art knowledge that ambient cured epoxies have significantly lower level of thrue-cure than epoxies cured at high temperatures. No data on release from ambient cured epoxy products have been provided and industry is asked to provide such information. More data are also needed for phenolic resins. However, no such data has been received from industy.

Due to the low vapour pressure release to the atmosphere is assumed to be low for processes performed at ambient temperature, while for high temperature processes there is a potential for significant releases. With a water solubility of 610 mg/l the potential for releases to the aquatic compartment becomes significant for processes including water.

The number of ptBP production sites is limited and monitoring data are partly available. A generic release calculation using the TGD / EUSES model has been performed for information and comparison with the site specific scenarios. For the local release calculations actual figures (e. g. release figures, WWTP data) have been used.

For the processing steps several users of the material have provided information. This information has been used to estimate the local releases of ptBP and to calculate local concentrations. However, to cover the releases from those sites where no information is available, generic scenarios according to the EU Technical Guidance Document have been applied.

3.1.1.1 Predicted environmental concentrations in water

3.1.1.1.1 Calculation of $Clocal_{water}$

The concentrations for the local water scenarios were calculated using the environmental releases estimated for the different use scenarios (TGD A and B tables) and using the equations set out in Chapter 3 Sections 2.3.7 and 2.3.8.3 of the Technical Guidance Document. Release estimations and calculations of local concentrations are performed according to the following equations:

$$Clocal_{inf} = \frac{Elocal_{water} \times 10^6}{EFFLUENT_{stp}}$$

$$Clocal_{eff} = Clocal_{inf} \times Fstp_{water}$$

$$EFFLUENT_{stp} = CAPACITY_{stp} \times WASTEWinhab = 2{,}000{,}000 \text{ l/d}$$

$$Clocal_{water} = \frac{Clocal_{eff}}{(1 + Kp_{susp} \times SUSP_{water} \times 10^{-6}) \times DILUTION}$$

$$DILUTION = \frac{EFFLUENT_{stp} + FLOW}{EFFLUENT_{stp}} = 10 \text{ [Default]}$$

$$Clocal_{water,ann} = Clocal_{water} \times \frac{Temission}{365}$$

Explanation of symbols:

$Clocal_{inf}$	Concentration in untreated wastewater [mg/l]
$Clocal_{eff}$	Concentration of the chemical in the STP-effluent [mg/l]
$Clocal_{water}$	Local concentration in surface water during emission episode [mg/l]
$Clocal_{water,ann}$	Annual average local concentration in surface water [mg/l]
$PEC_{local(water)}$	Predicted environmental concentration during episode [mg/l]
$PEC_{local(water),ann}$	Annual average predicted environmental concentration [mg/l]
$PEC_{regional(water)}$	Regional concentration in surface water [mg/l] (Section 3.1.1.1.2)
$Elocal_{water}$	Local emission rate to (waste) water during episode [kg/d]
Temission	No of days per year that emission takes place [d/year]
$Fstp_{water}$	Fraction of emission directed to water by STP [For p-tert-butylphenol = 0.12 according to TGD in case 10d window fulfilled and 0.31 when 10d window is not fulfilled, see section 3.1.3.2]
$EFFLUENT_{stp}$	Effluent discharge rate of stp [l/d]
$CAPACITY_{stp}$	Capacity of the STP [10,000]
$WASTEW_{inhab}$	Sewage flow per inhabitant [200 l/d]

DILUTION	Dilution factor [Default 10]
FLOW	Flow rate of the river [l/d]
Kp_{susp}	Solids-water partitioning coefficient of suspended matter [58.2 l/kg EUSES]
$SUSP_{water}$	Concentration of suspended matter in water [15 mg/l]

In calculating the local PECs the regional PEC is added to the local concentrations. In this instance the regional PEC is taken as a background concentration. For processes where there are no releases to water the PEClocal is the same as the PECregional.

3.1.2 Environmental releases

At present, this risk assessment has estimated releases from the production and processing stages of ptBP and from the use of polycarbonate products. A scenario has been attempted describing the release from land filled polycarbonate waste to illustrate the magnitude of the potential release through this source. PEC –values have only been estimated for the aquatic compartment as partition models show this to be the main compartment of interest.

3.1.2.1 Release from production

There are 3 production sites identified. Site-specific information is given below.

Production Site A:
Emissions during production are zero for production site A. A strictly controlled closed system is used. No wastewater is produced during the production process.

Production Site B:

Detailed information is available for site B. All waste water is treated in the local WWTP. In 2005 a total amount of 18994 m^3 waste water was produced. The WWTP treats both industrial and public waste water leading to a high dilution of receiving waste water streams from site B. The waste water is treated in a subsequent twofold biological treatment. At the 1st step a biological treatment of industrial wastewater takes place and the 2nd step treats the outflow of the 1st biological treatment plus public (non-industrial) waste water.

The first biological treatment occurs after dilution with further industrial water originating from other local companies via a big buffer tank. The inflow stream from all industrial sites was 2.49 mio m^3 in 2005.

The following scenario applies:
Average measured concentration of ptBP in outflow of site B: 16.7mg/l (2005 figures)
Dilution factor before first biological treatment: 132
PEClocal WWTP inflow before 1st treatment: 0.12 mg/l
A further dilution with public waste water of 3.01 Mio m^3 total in 2005 occurs before the second biological treatment, amounting to a total of 5.5 Mio m^3 per year. The following scenario applies under the assumption that the biological degradation only occurs during the second biological treatment.

Dilution factor before second biological treatment: 2.2
PEClocal inflow STP 2nd treatment: 0.055 mg/l

Removal in WWP 69 % (readily biodegradable substance, not fulfilling the 10 day window). The average volume stream of the receiving river water is 1041 m^3/s, the 10th percentile is approx 539m^3/s. A dilution factor of 3073 is calculated as based on WWTP outflow and the 10 percentile receiving water flow (exceedance over 90% of the year). However, according to the TGD the maximum dilution factor should be 1000.

The local concentration for the aquatic compartment can be calculated as follows:

Number of production days:	300 (TGD)
Estimated release to WWTP:	1.0 kg/d (actual data)
Size of WWTP:	18,333 m^3/d (actual data)
Average flow of receiving river:	539 m^3/s (10^{th} percentile; actual data)
Dilution factor:	1000 (maximum TGD default)
Removal rate in WWTP:	69 % (TGD, based on ready biodegradation failing the 10 day window)

Effluent concentration prior to dilution in receiving river: 17 ug/l

Effluent concentration after dilution: clocal = 0.02 ug/l

All sewage sludge from the WWT is incinerated.

Production Site C:
The release to air was reported to be 0.28 t/year during production of ptBP.
According to industry no emissions of ptBP to water occurs since the wastewater is incinerated on site.

Modelled Exposure data
PtBP is produced at 3 different sites in Europe. Information is available for all production sites. Calculation of releases using TGD default values is conducted only for information and comparison with the site specific emission scenarios. As in 2001 there were only 3 producers in Europe and by now there are only 2 producers a local tonnage of 50% of the total EU production has been chosen as a worst case situation.

Production volume: 12,600 t/a
Emission factors are taken from the TGD, table A1.1, assuming production of basic chemicals (IC2) with main category 1b.
Emission factor to waste water: 0.003
Emission factor to soil: 0.0001
No. of processing days: 300

Local concentration in the receiving water:

Release to wwtp:	12,600 t/a / 300 days * 0.003 = 126 kg/d
69 % removal in wwtp; release to surface water:	39.1 kg/d
Dilution in wwtp:	39.1 kg/day / 2000 m^3/day = 19.5 mg/l
Local surface water concentration (dilution 10)	1.95 mg/l

The local surface water concentration of ptBP at site B, calculated with site specific data, is several orders of magnitude lower than those from the generic scenario. This is due to the high generic release factor to water.

3.1.2.2 Release from formulation

In the Technical Guidance Document, formulation is defined as the stage where the chemical is combined in a process to obtain a product or preparation. For ptBP this stage of the life cycle is not relevant as no such step is thought to occur between production and processing.

3.1.2.3 Release from industrial/professional use

a) Use of ptBP as chain terminator for polycarbonate synthesis

There are 3 sites and information is available for all sites.

Most polycarbonate is produced in fully contained, closed systems by an interfacial polymerisation process utilising phosgene and bisphenol-A as starting materials. Three manufacturing locations (two companies) in the EU hereby use ptBP as a chain-terminating agent. All emission data have been reported by all 3 sites and the emission data are as follows:

Location A:

PtBP is used as a co-monomer for polycarbonate production. The polycarbonate contains 1 - 3 wt % of reacted ptBP, bound into the polymer chain.

The residual concentration of ptBP was measured. No free ptBP was detectable with detection limits of 5 ppm.

Polycarbonate production occurs in an automated closed system in a continuous process.

A biological wastewater treatment plant is available on site. The concentrations in the influent as well as the effluent have been monitored. The total amount of ptBP released with the WWTP effluent is calculated to be 44.4 kg/year.

The concentration in the effluent is 1.3 µg/l. The flow rate of the ptBP containing effluent is 94145 m^3/d. The overall size of the WWTP is 120000 m^3/d. The average flow of the receiving water is 720 m^3/s, and the low flow rate (10 percentil) is 288 m^3/s.

The low flow dilution factor therefore is about 207, resulting in a local ptBP concentration of about 6.3 ng/l.

Data and calculations:

Influent concentration (measured, 2001):	0.1679 mg/l
Volume stream of influent:	3651 m^3/d
Effluent concentration (measured, 2001):	0.0013 mg/l

Volume stream of ptBP containing effluent: 94145 m^3/d

Size of WWTP: 120000 m^3/d

Average flow rate of receiving water: 720 m^3/s = 62.208.000 m^3/d

Low flow rate of receiving water (10 percentil): 288 m^3/s = 24.883.200 m^3/d

Dilution factor = low flow rec. water/size of WWTP = 207.36

C_{local} = effluent concentration/dilution factor = 0.0063 µg/l

(For the PEC_{local} the regional PEC has to be added to the C_{local})

The concentration of ptBP in the receiving river due to the production of polycarbonates is 6.3 ng/l.

Emissions to air at location A are reported to be zero (fully contained system).

The sludge of the WWTP is incinerated on site. Emissions to soil via sludge disposal therefore do not occur.

Location B:

Detailed information for location B is available as well. An on-site biological waste water treatment plant is available. The production effluent is treated in an activated charcoal adsorption bed, before it enters the wastewater treatment plant. In the reaction process, p-tert-butylphenol reacts almost immediately as a chain terminator for polycarbonate. On top of that, p-tert-butylphenol has a great affinity to the organic phase of the reaction mixture and, as such, is not present in the alkaline Bisphenol A-in-water phase.

The concentration in the WWTP effluent is below 0.0044 mg/l. The volume of the effluent (size of WWTP) is 13224 m^3/d.

The net flow of the receiving water is 100 m^3/s.

(Mean low water flow rate of the receiving river is 4630 m^3/s, mean high water flow rate of the receiving river is 4730 m^3/s).

Data and calculations:

WWTP influent concentration (measured): < 1 mg/l

Volume stream of influent: 2904 m^3/d

Effluent concentration (measured): < 0.0044 mg/l

Size of WWTP: 13224 m^3/d

Net flow of receiving water: 100 m^3/s

Mean low water flow rate of receiving river: 4630 m^3/s

Mean high water flow rate of receiving river: 4730 m^3/s

Dilution factor: 653 (net flow of r. water/Size of WWTP)

C_{local} = effluent concentration/dilution factor = < 0.0067 µg/l

(For the PEC_{local} the regional PEC has to be added to the C_{local})

The concentration of ptBP in the receiving river due to the production of polycarbonates is lower than 6.7 ng/l.

Emissions to air at location B are reported to be zero (fully contained system).

The sludge of the WWTP is incinerated on site. Emissions to soil via sludge disposal therefore do not occur.

Location C:

Detailed information for location C is available as well. An on-site biological wastewater treatment plant is available.

The ptBP concentration in the effluent was monitored. The concentration was found to be 0.00024 mg/l. The size (volume stream) of the WWTP is 25800 m^3/d. The mean flow rate of the receiving river is 2740 m^3/s, the low flow rate (10 percentil) is 1930 m^3/s. A dilution factor (low flow) of 6463 can be calculated. A local ptBP concentration of about 0.037 ng/l can be calculated.

Data and calculations:

Effluent concentration (measured):	0.00024 mg/l
Size of WWTP:	25800 m^3/d
Average flow rate of receiving water:	2740 m^3/s = 236736000 m^3/d
Low flow rate of receiving water (10 percentil):	1930 m^3/s = 166752000 m^3/d
Dilution factor = low flow rec. water/size of WWTP:	1000 (maximum TGD default)

C_{local} = effluent concentration/dilution factor = 0.00024 µg/l = 0.24 ng/l.

The concentration of ptBP in the receiving river due to the production of polycarbonates is 0.24 ng/l.

Emissions to air at location C are reported to be zero (closed system, use of phosgene).

The sludge of the WWTP is incinerated on site. Emissions to soil via sludge disposal therefore do not occur.

Conclusion:

Since emission data are available for all polycarbonate production sites where ptBP is used; no release calculations using the TGD/EUSES default parameters for this scenario need to be performed. The risk assessment and risk characterization can be based on site specific data.

The local concentrations of ptBP in surface water are 6.3 ng/l (location A), 6.7 ng/l (location B), and 0.24 ng/l (location C). Emissions to air do not occur. Sewage sludge is incinerated on site at all 3 locations; therefore emissions via disposal of sludge do not occur.

b) Release during polycarbonate processing (extrusion and injection moulding)

The most commonly used processing operations for conversion of polycarbonate resins into finished articles are extrusion, used for the production of profiles, films and sheets, and injection moulding for the production of a variety of other articles e.g. DVDs and CDs.

Processing of polycarbonate may lead to degradation and formation of free monomers if incorrect operating conditions are employed. According to information from the polycarbonate producers they issue written guidelines and provide technical assistance to downstream users. This supporting information deals with processing parameters like temperatures and pre-treatment of the polymer prior to conversion (i.e. drying). It is assumed that there are a large number of sites. Provided that the guidance is followed the formation and release of ptBP due to degradation during processing of polycarbonate should be negligible. Measurements on the release of airborne ptBP during polycarbonate processing are reported in the occupational exposure part of the Risk Assessment report. According to these studies no airborne ptBP has been detected in the vicinity of the processing equipment at the detection limit for the measurements (for example at a detection limit of 0.01 mg/m^3 for sheet extrusion processes) (tables 7 and 8 of the occupational exposure part of the risk assessment report).

c) Release during use of polycarbonate products

Release of ptBP from polycarbonate products may occur through two different routes, by either hydrolysis of polymer chain terminal or by migration of residues of non reacted ptBP.

<u>Release from polycarbonate products due to hydrolysis of chain terminal</u>
Hydrolysis of a polymer may potentially give rise to the monomers it was formed from, in this case ptBP. The most likely application of polycarbonate that can result in possible hydrolysis of the polymer is thought to be its use in solid and multi-wall outdoor applications, where weathering effects may lead to the breakdown of the polymer. One polycarbonate producer made an investigation regarding the weathering of polycarbonate sheet samples and the loss of bisphenol-A from these samples (see RAR for bisphenol-A for description). Similar tests to estimate the release of p-tert-butylphenol from polycarbonate used in outdoor applications have not been conducted. However, the tendency of hydrolysis leading to a possible release of p-tert-butylphenol from polycarbonate have been estimated based on the investigations regarding bisphenol-A. The weight ratio of bisphenol-A/p-tert-butylphenol-units in polycarbonate terminated with p-tert-butylphenol used for sheet production is about 50/1. As the generation of the bisphenol-A monomer and p-tert-butylphenol monomer from the polycarbonate backbone both involve the same chemical process, i.e. hydrolysis of the carbonate links, it can be assumed that the ratio of free bisphenol-A versus p-tert-butylphenol generated during degradation will be similar to their initial ratio in the polymer. Therefore the annual loss rate estimated for bisphenol-A of 0.15 mg/m^2 would translate into a loss rate of 0.003 mg p-tert-butylphenol / m^2 / year.

Based on the quantities of polycarbonate sold in Europe for the various outdoor sheet applications the total surface area of outdoor sheets produced from p-ter-butylphenol terminated polycarbonate is estimated at 6.9 km^2. This would result in a release of 20 g/year taking the release factor of 0.003 mg/m^2 into account. Assuming a 10 year life time of the products would increase the estimated release of ptBP to approximately 200 g/year. Even if the quantity of polycarbonate used in sheeting is considerably underestimated, releases due to weathering effects are likely to be negligible.

Release from polycarbonate products due to migration of ptBP residuals
According to information from industry analytical determinations have shown that ptBP residuals are not present in polycarbonate resins and articles at a 5 ppm limit of detection.

According to Fabes (2003) "the transfer of ptBP from the polycarbonate to the environment in an open system is independent on the contacting medium as long as the diffusion in the polymer is the rate determining step. This assumption is fulfilled for ptBP because on the one hand the diffusion of low molecular weight organic components in polycarbonate is very low and on the other hand the vapour pressure is high enough to facilitate the evaporation into the gas phase and/or the water solubility is high enough to facilitate the transfer into an aqueous phase. The migration rate of low molecular weight components from PC is very low. In the case of ptBP after 1 year at 20 ^{o} C 0.5 % of the initial amount would be released into the environment and after 10 years 1.5 %. Increases in temperature with 10 ^{o}C will approximately double the migration rate".

According to the knowledge of industry there are no significant quantities of water bottles on the market based on ptBP-polycarbonate. Releases from this use (e.g. bottle washing) have therefore not been considered in this RAR.

Therefore only polycarbonates used in outdoor applications are considered relevant for the migration release estimates. Sales to the European market (outdoor and indoor application) is approximately 160,000 tons/year of which outdoor applications is estimated to be 19,000 tons/year. Moreover, only the outer side of the solid sheets or the hollow multi wall is exposed to the outdoor environment. Therefore the polycarbonate mass corresponding to the total surface exposed to outdoor is about 4400 tons. According to Fabes (2003) a migration of 0.5 % of unreacted ptBP may occur after 1 year, giving a release of 110 g/year. Assuming a 10 year life time of products would increase estimated release of ptBP to approximately a total of 330 g after 10 years. As this is a wide dispersive release it is considered negligible for risk assessment purposes.

d) Use of ptBP in phenol/formaldehyde resins production

Emissions during production of phenol/formaldehyde resins are normally limited.

Because ptBP is normally handled in a closed system or with dust collection, there is little likelihood of direct emission to atmosphere under normal conditions. Either IPPC or current national regulations restrict releases and these will be prevented by (e.g.) wet scrubbing or dust filtration.

Data and information regarding the use and exposure were received from 8 phenolic resin producers in 2001. Although only a limited number of phenolic resin producers responded, the information is helpful for an overview of the exposure situation.

Site 1: No emissions to wastewater, air or soil according to industry.

Site 2: No data concerning emission to the atmosphere is available. By comparison with phenol, that is used in the process as well, the emission is expected to be < 30 kg/year. Due to much lower volatility of ptBP, this estimate is likely to be an overestimation.

A biological WWTP is available on site. However, this WWTP only treats water from rainfall onto the plant.

The process water produced during resin production is treated by commercial, licensed waste disposal companies. Normally effluents are collected separately, depending on their phenol concentration. Limited information is available on the ptBP concentration of the combined trade effluent. This trade effluent is stored off-site, chemically treated and mixed with other waste streams before released to the sewer. It is then further diluted and treated by a municipal sewage treatment plant. In a single sample of the untreated effluent (before combining with other effluents) the concentration was found to be 130 ppm.

Site 3: No emissions of ptBP to air occur during the production of resins. No emissions of ptBP to water occur since the wastewater is incinerated on site.

Site 4: Emissions to the atmosphere do not occur.

The wastewater is treated on-site (activated carbon treatment) before being discharged to a municipal biological waste water treatment plant. The amount released to the WWTP was estimated to be 2 kg in the year 2000. The flow through rate of the WWTP is 300 m^3/d.

Based on these data the local concentration in the receiving river can be calculated to be 0.56 µg/l.

Discharge to WWTP = 2 kg/year or 5.5g/d

Influent = 0.018 mg/l

Removal rate = 69 % (according to TGD, ready biodegradability, failing 10d window)

Effluent = 5.6 µg/l

Dilution factor = 10

C_{local} = 0.56 µg/l

Site 5: For site 5 only limited information is available. Production of phenolic resins takes place in an automated batch process in a closed system. The number of processing days is known but no data is available on environmental emissions. It is only known that the receiving surface water is an estuary. For calculation of clocal the input parameter from the generic scenario have been applied (emission factor of 0.0023 and 69% removal in a wwtp and a dilution factor of 100 as the emissions are directed to an estuary). The emission factor of 0.0023 may be too high for a closed-system batch process but as no information on releases of ptBP to the aquatic environment is available at the moment this calculation has to be considered as a worst case until site specific data is available. As the tonnage used at this site is considered confidential no clocal is presented here. According to recent information from industry during the risk reduction phase site 5 , originally reported amongst the phenol/formaldehyde resin production sites, uses ptBP in the production of tri-aryl phosphate esters. The emission scenario had been considered to be comparable to the phenolic resins production scenarios.

Site 6: No information on the production process and on emissions to the environment has been provided by industry. The tonnage used at this site is very low but no information on the number of processing days is available. Using the TGD default value of 300 days per year does not seem to be appropriate due to the low tonnage and therefore no clocal could be calculated.

Site 7: PtBP is completely used for the production of phenolic resins. An industrial wastewater treatment plant is available on-site. The flow rate of the WWTP is 300 m^3/d. The concentration in the effluent was determined to be 5 µg/l, resulting in an annual release to surface water of 450 g. Based on this information a local concentration of 0.5 µg/l can be calculated (applying a dilution factor of 10).

C_{local}=0.5 µg/l

Site 8: PtBP is completely used for the production of phenolic resin based additives for the rubber industry (accelerators). The products are produced in a batch process in a closed, semi-automated system at approximately 200 days per year. No emissions to air occur.

A WWTP is available on-site. Influent and effluent concentrations have been determined in 2000. The effluent concentration was below 0.01 mg/l (limit of detection). The volume stream of influent is 200 m^3/d, resulting in a release of approximately 2 t/year (estimated). The volume stream of the effluent is 2000m^3/d. Based on the effluent concentration a release of below 4 kg/year can be estimated.

The mean flow of the receiving river is approximately 2500 m^3/s (but varying due to tidal influence), resulting in a dilution factor (based on mean flow) of about 108,000, however, the maximum dilution factor according to the TGD is 1000.

Based on the effluent concentration of < 0.01 mg/l the local concentration in fresh water is below 0.01 µg/l.

C_{local} < 10 ng/l

Marine assessment:
As the flow of the river is varying due to tidal influence this site seems to emit its treated waste water to a coastal zone and a marine risk assessment is considered necessary. A dilution factor of 1000 for discharges to a coastal zone is chosen, instead of 100 as recommendet by the TGD, as specific information on the dilution is available for this site. The dilution factor of 1000 represents anyhow a very worst case because the outflow of the WWTP is emitted to a river (with a dilution factor of about 100,000) which then flows into the sea instead of presuming direct discharge to a coastal zone. For a marine risk assessment the same C_{local} is used as for the fresh water assessment ($C_{local, marine}$ < 10 ng/l).

EPRA water monitoring program 2005/2006

EPRA (European Phenolic Resins Association) conducted an Alkylphenol Water Monitoring Study in 2005/2006 in order to determine emissions of ptBP from phenolic resin production sites to the aquatic environment. Also data on other alkylphenols have been obtained, but are not reported here.

There are a number of phenolic resin production sites that utilise alkylphenols in Europe. From discussions with EPRA during the planning of the monitoring program it became clear that it was not possible to consider the extent of releases of alkylphenols from all relevant phenolic resin production sites in Europe.

Number of sites:
Not all sites using ptBP in the production of phenolic resins are EPRA members. In the present monitoring program 3 phenolic resin production sites organised in EPRA participated. Two companies organised in EPRA reported not to produce water emissions. Two companies have exited the business, whereof one exited already more than 6 years ago and had never reported tonnages to the EU risk assessment program. Therefore this site is not seen to be relevant regarding the ptBP volume in resins due to its early exit.

The 3 sites participating in the monitoring program use variable amounts of ptBP and they all use batch processing. One of the sites produces constantly over the year. At two sites, waste water is treated in biological waste water treatment plants, at the third site the waste water is treated by an activated carbon treatment before being released to a municipal waste water treatment plant. This activated carbon treatment works by pumping the pre-filtered waste waters through an in-line arrangement of tanks with activated carbon, which process is absorbing the organic substances. The monitoring study involved measuring the water concentrations of ptBP in a number of samples taken before and after waste water treatment.

Sampling:
The collection of the samples for the monitoring exercise at each site was carried out by operatives of the company involved. At each of the three sites a series of samples of the influent to and final effluent from the wwtp/waste water treatment were collected over a one week period when ptBP (and potentially other alkylphenols) were being used in the phenolic resin production. In the monitoring exercise 24 hours composite influent and effluent samples were collected. Once the composites had been collected on a given day one litre aliquots of the samples were sub-sampled into clean glass bottles and preserved with concentrated hydrochloric acid (37%) until the pH of sample was 2 or less. The samples were then stored at 4°C until the exercise at the site was complete and they were transported to the analytical laboratory. The samples were extracted with dichloromethane and analysed with GC-MS. The limit of detection was 1 µg/l, both for influent and for effluent samples. Clean water from the sites was treated similarly and analysed in order to check for contamination of samples during sampling and handling.

Results:
Influent concentrations to the waste water treatment facilities at all three sites varied from < 1 µg/l (detection limit) to above 50 mg/l. Effluent concentrations were in the range of < 1 µg/l and about 10 µg/l.
Elimination rates of the waste water treatment plants were above 90%, except for two single measurements of one site, with elimination rates between 60 and 80%. However, the effluent of the waste water treatment of this site undergo further treatment in a municipal waste water treatment plant before being released to receiving waters. This can be expected to lead to overall elimination rates in the range of about 90%. These high elimination rates from the sites having industrial wwtps are considered to be achieved by microorganisms, which are adapted to ptBP and partly very long retention times of the waste waters in the treatment plants. However, elimination rates could not always be determined. Due to dilution of the effluents from phenolic resin production with other effluents, not containing ptBP, the measured inflow and outflow values were in some cases found to be below the detection limit. The discharges from the waste water treatment plants received further dilution either in the receiving surface water or if released to a sewer system and ultimately to a municipal STP. The resulting PECs surface water are in the range of < 1 ng/l to 29.5 ng/l. These values do

partly not take into account further degradation in a municipal STP if the discharge is released to a municipal sewer system before being ultimately released to receiving surface water.

Multiplying the highest measured ptBP concentration in the influent to the wwtp during the time when ptBP was used at the sites with the average volume of the waste water inflow to the wwtp at the three sites, respectively, gives the maximum daily amount of ptBP emitted for each of the sites. Based on the daily tonnage used at the site the daily release of ptBP from phenolic resin production, the emission factors, can be estimated. These emission factors for the three sites are in the range of $9.6x10^{-6}$ to 0.0039.

Only three plants have been involved in the monitoring program using different production processes and waste water treatment, having different production volumes, in- and outflow concentrations, dilution factors etc. Therefore all site specific details regarding the three sites are considered confidential and can be found in a confidential appendix.

Situation with regard to phenolic resin production in 2005

According to information from EPRA the number of phenolic resin producers using ptBP in 2005 has declined to 15-20. However, other information from the ptBP producers confirm that the number of sites reported in 2001, which was 25-30, is still valid in 2005. It has therefore been assumed that a number of 20-25 sites would be most realistic. Regarding the tonnage used in the production of phenolic resins industry recently confirmed that the tonnage of 15,000 t/a, which was reported in 2001, is about the same in 2005.

EPRA companies – such having emissions to waste water and such not producing emissions to waste water – are estimating now to cover basically 47 % of the market, or about 7,000 t/a out of a total of ca 15,000 t/a used in the phenolic resin production. Of the 3 companies which now have taken part in the EPRA water monitoring program 2005/2006 one participated already in the CEPAD questionnaire from 2001. In the questionnaire from 2001 8 sites provided exposure information. In the meantime site 2 has ceased production. In 2005 exposure information via EPRA is available for 6 sites, some of which already reported exposure information in 2001. For some companies which reported in 2001 no information is available as to the situation in 2005. With information available for a total of 9 phenolic resin production sites (combined 2001 and 2005 situation) information for about 14 sites, with respect to tonnage and exposure situation, is missing.

As the total tonnage is approximately the same in 2005 as it was in 2001 no data on production processes and emissions to the environment for about 7,500 t ptBP in the phenolic resins production are available. Therefore a generic scenario has to been conducted.

Generic assessment for a phenolic resin production site

Assuming that there are 14 sites producing phenolic resins lacking exposure information would result in an average use volume of 536 t/a for each site. Taking into account bigger companies and based on information received from industry in the recent past it seems realistic that the worst case scenario should cover at least about twice to threefold of the average. This gives a local worst case tonnage of approximately 1,000 to 1,500 t/a in the generic scenario. Industry confirmed that a tonnage of 1,000 – 1,500 t/a for a local worst case site can be seen as realistic. Regional release is set equal to local release.

Based on available monitoring data from three sites of the monitoring program an average emission factor to water from the site having the highest emissions of 0.0023 is assumed.

The TGD emission factor for IC 11, Type I (Monomers) as shown in table A3.10 of the TGD is 0.001, the release factor to air is 0.00001 and to soil 0. When comparing the TGD value for release to surface water with the average emission factor of the site having the highest emissions it becomes clear that the TGD value does not necessarily overestimate the emission situation to waste water treatment plants. However, the emission factors of the other sites are well below the TGD default factor.

Worst case use/site: 1,500 t/a
Release to WWTP: 1,500 t / 300 days * 0.0023 = 11.5 kg/d
Concentration in WWTP (2000 m^3): 11.5 kg/d / 2000 m^3/d = 5.75 mg/l
Release to surface water after 69 % removal: 1.78 mg/l
The daily local release to surface water is: 3.57 kg/site/d
Following dilution (10): Clocal= 178 µg/l

The description of the situation with regard to phenolic resin production in 2001/2005 refers to the European Union as it was before its extension in May 2004.

Release from ptBP formaldehyde resins used in polychloroprene adhesives

This resin has a maximum free ptBP content of 4 % by weight. A test was performed with a polychloroprene adhesive containing 6.25 % of a phenol formaldehyde resin with 1.8 % free ptBP. Total concentration in this adhesive was therefore estimated to be 0.11 %. Chemical analysis showed a concentration of 0.13 % ptBP. The adhesive was then left to dry for 7 days at room temperature and a new analysis showed free ptBP concentration of 0.12 %. The conclusion was drawn that ptBP does not evaporate to a significant degree from adhesives. However, the information provided in this regard is insufficiently documented (no methods described).

e) Use of ptBP in epoxy resins production

Only very limited information regarding the releases to the environment is available from epoxy resin producers. The release to the aquatic environment is reported to be zero. Release to air is reported to be either zero or very limited (related to transfer of material from 25 kg bags to reactors).

However, no site specific information is available and industry was therefore asked to provide more exposure information for the epoxy resin production. However, no site-specific information has been obtained but only qualitative descriptions of the productions process used by some customers. This information is presented under the description of the four sub-scenarios below. However, this information was not considered sufficient for being used in the revision of the PECs.

Industry stressed that the environmental exposure may differ for the use of ptBP in the four sub-scenarios described in chapter 2.2.2.3 and that therefore the use of only one single exposure scenario for epoxy resins would not reflect the actual situation. According to

information from industry from 2001 1,500 t ptBP was used in the epoxy resin area in 2001. It has been assumed that this figure is also valid for the situation in 2005. As no other information is available we allocated 400 t/a to sub-scenario 1, 2 and 3, respectively and 300 t/a to sub-scenario 4, as this scenario was considered of minor use according to industry. For all sub-scenarios regional release is set equal to local release.

Sub-scenario 1

For sub-scenario 1 (Starting material in the manufacturing of ptBP glycidylether (ptBP-GE) used as reactive diluent / thinner in epoxy resin systems) industry suggested using the default scenario "chemicals used in sythesis" as no further data is available. On the other side we also received the information from industry that various customers incinerate their waste water, therefore not having emissions to water. However, as it is not clear whether incineration is the standard procedure for all sites processing ptBP-GE IC3/UC33 default values from the TGD have been used for calculation of the PEC. Industry suggests further adapting the local tonnage of 225 t/a used in the former "general" epoxy scenario since only a part of ptBP used in the epoxy industry is used in this sub-scenario. Although this seems quite reasonable a tonnage of 200 t/a has been used as a local tonnage, applying a fraction of 0.5 to the total tonnage of 400 t/a used in the sub-scenario 1, as no information is available on how big a typical sub-scenario 1-site could be. The choice of the size of the site and the TGD release factors can be considered as a worst case situation as long as no site-specific information is available.

IC 3 / UC 33

Total volume:	400 t
Fraction of main source:	0.5 (leads to a local tonnage of 200 t)
Release fraction to waste water:	0.02
Release fraction to air:	0
Release fraction to soil:	0.0001
Number of emission days:	0.4f * T (= 80 days)

The daily local release to soil is:
400 t * 0.5 * 0.0001 / 80 = 0.00025 t/site/d = 250 g/site/d

The daily local release to waste water is:
400 t * 0.5 * 0.02 / 80 = 0.05 t/site/d = 50 kg/site/d

The local concentration can be calculated to be:

Removal rate in WWTP:	69 %
Size of WWTP (TGD default):	2000 m^3/d
Dilution factor (TGD default):	10

The daily local release to surface water is: 15.5 kg/site/d

Concentration in effluent:	7.75 mg/l
After a default dilution of 10:	Clocal= 775 µg/l

Sub-scenario 2 and sub-scenario 3

Sub-scenario 2 (use as an accelerator in hardening agents for epoxy resins based on amines) is, according to information from industry, a simple mixing scenario where no process water is involved. For the TGD default calculations industry has therefore proposed to use IC 11 = Polymers Industry, Table A 3.11 = Polymer processing, type V = curing agent.

The process in sub-scenario 3 (starting material in the production of "Mannich bases" used as hardening agents for epoxy resins) is also described by one producer as a process without process water. Water which is formed in the reaction process will be removed via distillation, treated separately and not be fed into the waste water treatment system. Exposure to surface water is, according to another producer, possible only due to reactor cleaning processes after batch production, however, data on concentrations in the effluent are not available. As it is unknown whether this description is valid for all Mannich bases production sites the same default assumptions have been made as in sub-scenario 2 where also no process water is involved (IC 11). A total tonnage of 400 t/a is assumed to be used for each of the two sub-scenarios.

IC 11 / UC 43

Total volume:	400 t
Fraction of main source:	0.25 (local volume 100 t/a)
Release fraction to waste water:	0.00005
Release fraction to air:	0.075
Release fraction to soil:	0.00001
Number of emission days:	0.4f * T (= 40 days)

The daily local release to soil is:
400 t * 0.25 * 0.00001 / 40 = 25 g/site/d

The daily local release to air is:
400 t * 0.25 * 0.075 / 40 = 188 kg/site/d

The daily local release to waste water is:
400 t * 0.25 * 0.00005 / 40 = 125 g/site/d

The local concentration can be calculated to be:

Removal rate in WWTP:	69 %
Size of WWTP (TGD default):	2000 m^3/d
Dilution factor (TGD default):	10
The daily local release to surface water is:	38.8 g/site/d
Concentration in effluent:	19.3 µg/l
After a default dilution of 10:	Clocal= 1.94 µg/l

Sub-scenario 4

For sub-scenario 4 (modifier/chain terminator in the manufacturing of epoxy resins) some qualitative information has been received. According to this information process water is only used for the washing step. The wash water is then treated in an on-site wwtp but no further information is available on in- and effluent concentrations. According to other information from industry this scenario is probably at least comparable to the scenario of production of phenolic resins, where emissions to water are controlled. However, no measured data are available and therefore the default scenario "chemicals used in synthesis" has been suggested by industry. A total tonnage of 300 t/a has been assumed to be used in this sub-scenario. A fraction of main source leads to a local tonnage of 150 t/a. During production releases to water are reported to be only relevant for parts of the process. Therefore the release fraction to waste water has been lowered by a factor of 4 from 0.02 (TGD default) to 0.005.

IC 3 / UC 33

Total volume:	300 t

Fraction of main source:	0.5
Release fraction to waste water:	0.005
Release fraction to air:	0
Release fraction to soil:	0.0001
Number of emission days:	0.4f * T (= 60 days)

The daily local release to soil is:
300 t * 0.5 * 0.0001 / 60 = 250 g/site/d

The daily local release to waste water is:
300 t * 0.5 * 0.005 / 60 = 12.5 kg/site/d

The local concentration can be calculated to be:

Removal rate in WWTP:	69 %
Size of WWTP (TGD default):	2000 m^3/d
Dilution factor (TGD default):	10
The daily local release to surface water is:	3.88 kg/site/d
Concentration in effluent:	1.94 mg/l
After a default dilution of 10:	Clocal= 194 µg/l

Release from products (cured epoxy-coatings)

As described in chapter 2 (see chapter 2.2.2.3) cured epoxy systems may still contain significant amounts of unreacted ptBP (up to 5-10 %). In general, high temperature cured epoxy formulations are not expected to release significant quantities because of low residual amounts of free ptBP. This applies especially for can coatings, where food approval requirements have to be fulfilled. However, it is state-of-the-art knowledge that ambient cured epoxies have significantly lower level of thrue-cure that epoxies cured at high temperatures. No data on release from ambient cured epoxy products has been provided and industry is asked to provide such information. However, no data on release from ambient cured epoxy products has been provided by industry.

f) Hydrogenation

PtBP is used to produce the alcohol via hydrogenation of the phenolic structure. The hydrogenation is done in a strictly controlled closed system under high pressure using hydrogen (highly explosive). Emissions to the environment are therefore unlikely to occur according to industry. Hydrogenation is performed at least at four different sites in Europe.

A major producer using more than 50 % for this use category has been contacted and responded with site specific information. The process is performed in closed tanks under very high pressure. There is no wastewater from the process and cooling water is circulated in a secondary cooling system without any contact with ptBP. No emissions to the environment of ptBP are therefore expected from this use.

g) Production of oilfield chemicals

PtBP is not used as such in the oil industry. PtBP/formaldehyde resins are ethoxylated and used as oilfield chemical. Therefore the environmental release of ptBP is restricted to the phenolic resin production process. No additional environmental releases of ptBP therefore are expected during the production of oilfield chemicals.

3.1.2.4 Release from life-time service

Releases to the environment during life-time are assumed to be negligible for ptBP. However, no data on release from ambient cured epoxy products are available.

3.1.2.5 Distribution

According to industry distribution is mainly by dedicated trucks and if tanks are cleaned this takes place at the production site, releases will therefore be included in site releases. A small part of the production volume of para-tert-butylphenol (flaked material) is marketed in so-called "big bags", containing about 400 - 800 kg. The big bags are owned by the ptBP producers and the downstream users send all of them back to the producer. The big bags are re-used several times until they are incinerated on site. According to industry the bags are never landfilled or disposed to other wastes. It is therefore unlikely that they end up in the environment. A minor part of the material is sold in 25 kg bags. The bags itself are not re-used but incinerated by the customers. Other customers use the german company RIGK (Gesellschaft zur Rueckfuehrung industrieller und gewerblicher Kunststoffverpackungen mbH). This is a company taking care of disposal of packaging made of plastic materials from industrial use. The used bags are not landfilled according to information from industry

3.1.2.6 Release from disposal

Direct disposal of ptBP to the environment is unlikely to occur. It is more likely that ptBP will reach the environment as part of a product. In the products ptBP is chemically reacted, however, some residual ptBP remains. The residual ptBP is not chemically/covalently bound in the matrix, but closely bound in the matrix. The matrix itself is completely insoluble in water. Releases, e. g. migration from the products are expected to be low (see section 3.1.1). According to Fabes (2003) the transfer of ptBP from the polycarbonate into the environment in an open system is independent from the contacting medium, as long as the diffusion in the polymer is the rate determining step. The diffusion of low molecular weight organic components in polycarbonate is very low but the vapour pressure of ptBP is high enough to facilitate the evaporation into the gas phase and/or the water solubility is also high enough to facilitate the transfer into an aqueous phase.

<u>Landfill</u>
Following the provisions of Directive 1999/31/EC (ref. EC (2003a).), old, uncontrolled landfills have to be closed in the future. It might be expected that required collection of leached fluids and the treatment of controlled landfills in the future will minimize any environmental emissions of ptBP from polycarbonate waste. The yearly amounts of polycarbonate sold to the European market have increased significantly in the recent years. However, following Council Decision 2003/33/EC coming into force July 2005, restrictions

on landfill disposal will be enforced. These restrictions are aiming a diversion of e.g. polymers from landfill and feeding those materials to recovery processes (e.g. mechanical or thermal). Accurate figures regarding the amounts of ptBP-based-polycarbonate disposed of by landfilling are not available. Neither do we have any experimentally generated data that could be used in estimating the current environmental releases of ptBP from landfilled polycarbonate. Since polycarbonate is a material that in the past years has found its applications mainly into goods with a medium- to long lifetime, the waste generated cannot be correlated to the contemporary production volumes of polycarbonate, but would need to be estimated from the historical sales/production data.
No comprehensive study to estimate the actual useful lifetime of polycarbonate has been undertaken with regard to its different end-use applications. In this report a period of ten years is assumed to be a plausible figure for the average time span between production and final disposal of polycarbonate.
An estimation is made in the table below where the approximate amounts of materials which have been sold to the European market from 1992 (the first year in which ptBP-based-polycarbonate was offered to the European market) up to 1995 (representative of the amount that will end up as waste in 2005, assuming a ten year life time).
The fraction of plastics waste disposed of by landfilling varies from country to country and by end use application. (ref. APME (2002)).

Taking into account the major applications of ptBP-based-polycarbonate which industry reported earlier (ref Cefic exposure questionnaire for users / producers: input Polcyarbonate producers) an average fraction of 65 % of the waste being disposed of via landfilling is assumed for the purpose of this estimation (ref EC (2003b)

Table 3-1: Estimation of polycarbonate waste deposited in landfills

Year of sales	Amount of ptBP-based Polycarbonate sold (x 1000 tons)	Year during which the polycarbonate material becomes waste (1)	Estimated yearly amount of waste allocated to landfill (2) (x 1000 tons)
1992	15	2002	10
1993	25	2003	16
1994	50	2004	33
1995	61	2005	40

(1) assuming a lifetime of the Polycarbonate article of 10 years.

(2) assuming a fraction of 65% disposed of by landfilling

Table 3-1 gives an estimation of amount of polycarbonate deposited in landfills. It indicates that by the year 2005 a total amount of 99000 tons will be accumulated in landfills. Fabes (2003) estimate that polycarbonate with 5 ppm ptBP leach 0.5 % of this the first year and in total 1.5 % in the course of 10 years. When polycarbonate sheets are landfilled, the two outer surface sides of multi-wall structural sheets can contribute to releases. According to information from polycarbonate producers, this is estimated to correspond to a fraction of about 50 % of the total polycarbonate waste volume. Assuming that residual ptBP is 5 ppm and that 0.15 % (= 1.5 %/10 years) of this is leached out each year would give a total release to water of 370 g/year. As this release is very dispersed (many landfills) and much of this also will end up in municipal WWTP, no local PEC is estimated for this scenario.

3.1.2.7 Summary of emissions

Releases to the environment are expected primarily to the aquatic compartment, but also to air and to a limited extent to soil. Emissions of ptBP to the different environmental compartments occur partly during production and processing of ptBP and from disposal of ptBP containing products as shown in chapter 3.1.2.

A summary of the local releases to the hydrosphere and local aquatic concentrations is presented in chapter 3.1.4. Releases to the terrestrial compartment and the atmosphere are summarised in chapter 3.1.5 and 3.1.6, respectively.

3.1.3 Environmental fate

3.1.3.1 Degradation in the environment

3.1.3.1.1 Atmospheric degradation

Photodegradation

In a study by Freitag (1984) ptBP was one of several chemicals tested with respect to photodegradation due to UV-light exposure. PtBP was applied on (100 ng/g) silica gel surface and exposed for 17 h to UV-light. A reduction of ptBP of 46.8 % was observed after 17 h.

OH-radicals degradation

Assuming $5x10^5$ OH molecules/cm^2 a half-life of 0.4 days was estimated by the AOP computer program (Syracuse Research Senter). Using AOPWin v1.09 which assumes a $1.6x10^6$ OH molecules/cm^2 a half-life of 0.131 days was estimated.

Conclusion with respect to residence time in the air compartment

PtBP will be rapidly removed from the air compartment through a combination of photodegradation and OH-radical degradation giving a half life of 0.4 days or less. This value will be used for EUSES calculations. In addition the water solubility of 610 mg/l will result in rapid deposition of any PtBP present in the atmosphere during rain.

3.1.3.1.2 Aquatic degradation (incl. sediment)

Aerobic biodegradation

A non-standard biodegradation test (Freitag, 1984) gave no degradation after 5 d.

According to a MITI II test (MITI, 1992), no biodegradation was observed in a test system inoculated with 100 mg/l of mixed sludge and 30 mg/l of ptBP after 14 days. No biodegradation is probably due to an inhibitory concentration of ptBP in this study combined with a long lag phase.

In a Material Safety Data Sheet from Huels dated 1992, biodegradation of ptBP is given as 45 % after 28 days. The test has been performed according to OECD 301E (DOC, modified OECD screening test). However, no test report is available and therefore no further details are known.

The aerobic biodegradation was tested in a DOC-Die-Away test according to OECD 301A (Huels AG, 1994). The study was conducted according to GLP. The test substance concentration used was 13 mg/l ptBP corresponding to 10.4 mg DOC/l. Inoculum from a predominantly municipal wastewater treatment plant was used. The DOC removal was found to be 98% after 28 days. According to this test results the substance can be regarded as readily biodegradable meeting the 10 day window criterion. Adsorption can be ruled out as a removal path as shown by DOC measurements after 3 hours. Natriumbenzoat was used as a reference control and achieved 99 % removal after 28 days, fulfilling the 10 day criterion. However, it

can not be excluded that the inoculum might have been adapted to ptBP as it was taken from a municipal WWTP in a heavily industrialised area where industry might be located using ptBP.

Aerobic biodegradation performed according to OECD 301 F, "Manometric Respirometry Test" was carried out with two levels of ptBP, 15 mg/l and 25 mg/l (NIVA, 2003c). The study was conducted according to GLP. The inoculum used was micro-organisms cultivated in an in-house activated sludge simulation unit and adaptation to ptBP has not taken place. There was a lag phase at both exposure concentrations before the degradation of the test compound was initiated. Biodegradation was 60 % for 15 mg /l ptBP and 42 % for 25 mg/l ptBP after 28 days.
That the observed lag phase actually is longer at 15 mg/l (16 days) than at 25 mg/l (12 days) indicates that the lag phase may not be related to toxicity but rather to adaptation. At 15 mg/l 10 % degradation is achieved between sample point day 16 and day 18. This means that the whole 10 day window is present within the test period of 28 days.
In the toxicity control, conducted at 25 mg/l ptBP, the reference compound aniline showed 35 % reduction of degradation after 14 days before becoming equal to the reference compound without ptBP. As the inhibition at 25 mg/l is low and temporary it can be assumed that it will be even lower at 15 mg/l.
According to the test results of this study ptBP should be regarded as readily biodegradable but failing the 10 day window criterion, although this has to be considered as a borderline case. The study shows that municipal sludge microorganisms need an adaptation period in order to be able to degrade ptBP rapidly.

In a report by Scharf & Sattelberger (1999b) of 17 STPs, the concentration of alkylphenols (4-tert-butylphenol, 4-sec-butylphenol, 4-tert-octylphenol, 4-tert-amylphenol and 4-nonylphenol), nonylphenolethoxylates, phthalates and organotin compounds were determined in the inflow and outflow of STPs. 24 hours integrated samples from in- and outflow of the STPs were collected at the same day (see Table 3-2). The samples were filtered before chemical analysis and the detection limit was 50 ng/l. The sampled STPs were mostly municipal with 3 industrial STPs included. However, the three industrial STPs are not included in Table 3-2, but only municipal STPs. The data presented in Table 3-2 represent unique samples. Seven out of 13 ptBP results are "greater than" values, because the concentration in the outflow was below the detection limit. Five values, where the concentrations in the outflow were not below the detection limit, show a removal between 3 and 53 %. In two of the STPs (number 3 and 13) there is a significant increase in the concentration through the plant.

Values from a similar study in Sweden are included in the same table. One result shows that the concentration in the outflow of the treatment plants was higher than in the inflow and the removal of the two other measurements is between 2 and 40 %.

The fact that in three cases the effluent concentrations are higher than the influent concentrations can be explained by the fact that the inflow and outflow of the STPs were measured on the same day. According the TGD the hydraulic retention time in the aeration tank of the STPs is about 7-8 hours. A variable inflow could explain this seemingly inconsistency. The increase could theoretically also indicate formation of p-tert-butylphenol through the degradation of other alkylphenols in the plants.

At site 3 and 13 of the Austrian STPS ptBP seems to be produced. Concentrations of 4-tert-octylphenol at these STPs give no clear indication that this substance degrades to ptBP. At

STP 3 efffluent concentrations of both 4-tert-octylphenol and ptBP were higher than influent concentrations. This STP seems to produce both ptBP (+142%) and 4-tert-octylphenol (+77%). At STP 13 ptBP seems to be produced while the concentration of 4-tert-octylphenol decreased by 71%. At STP 7 ptBP concentration decreased by 50 % while 4-tert-octylphenol seems to be produced (inflow < 50 ng/l and effluent 196 ng/l). 4-sec-butylphenol and 4-tert-amylphenol concentrations in the influent and the effluent samples were below the detection limit of 50 ng/l.

In the Swedish report (Hajslova, 2002) in- and outflow concentrations of 4-tert-butylphenol, 4-tert-octylphenol and 4-nonylphenol in STPs were measured. These measurements gave no indications that 4-tert-octylphenol or 4-nonylphenol was degraded to 4-tert-butylphenol to a significant amount.

Other complex alkylphenols, as e.g. p-C12-alkylphenols, are expected only to be degraded to a very low extend.

In general it can be concluded that available data do not support the assumption that ptBP is a degradation product of other alkylphenols in these STPs. Another alkylphenol, 2,4-di-tert-butylphenol, is a HPV chemical but is not expected to biodegrade to 4-tert butylphenol for the following reasons: 2,4-di tert butylphenol is mainly used in chemical synthesis and is completely consumed , therefore it is not expected to be present at significant levels in STPs. Technically, a de-alkylation of 2,4-di tert butylphenol is only possible under extreme conditions (at around 200 °C under very acidic conditions and catalysts); it is not expected that this can be achieved by enzymatic mechanisms. Furtherone from its chemical structure it would be expected that metabolism occurs mainly via the the phenolic OH group or to a minor extent via oxidation of the alkylchains. An oxidative demethylation (mainly methyl and ethyl moieties) is known to happen by metabolic enzymes but only from ether or aminic functions. Metabolic de-tert-butylation is not expected and definitely not from aromaic systems. No respective literature reference could be found. A literature screen has not given any indication of p-tert butylphenol being formed from 2,4-di tert butylphenol under environmental conditions.

According to the TGD Appendix II “Fate of chemicals in a waste water treatment plant based on the Simple Treat model” the expected removal of ptBP in a STP is 88 %, assuming readily biodegradable meeting the10 day window criterion. Simple Treat predictions assuming ready biodegradability without passing the 10 day window criterion result in a removal of 69 % of ptBP in a STP. Values in Table 3-2 which are above the detection limit, do not support high removal in STPs corresponding to a readily biodegradable substance, fulfilling the 10 day window criterion.

Table 3-2: Reported concentrations of ptBP in inflow and outflow of STP in Austria

WWTP in Austria (Scharf & Sattelberger, 1999b)			
WWTP	**Inflow ng/l**	**Outlflow ng/l**	**% removal**
1	153	90	41
3	88	213	-142
4	101	<50	>50
5	226	<50	>77
6	241	185	23
7	887	448	50
8	89	<50	>44
10	91	<50	>45
11	67	65	3
12	104	<50	>51
13	110	154	-40
14	124	58	53
15	63	<50	>20
16	816	<50	>94
Swedish study (Hajslova, 2002)			
Simsholmen (6.11.01)	59	58	2
Simsholmen (14.11.01)	46	52	-13
Huskvarna (5.11.01)	98	59	40

As there are conflicting results on the biodegradation behaviour of ptBP the biodegradation behaviour of other structurally similar alkylphenols has been examined. Data are taken from the UK report on "Prioritisation of Alkylphenols for Environmental Risk Assessments", from "Environmental risk evaluation report: para-C12-alkylphenols from UK, from the BUA report 231 on 2-tert-Butylphenol and from the environmental risk evaluation report on 4-tert-Octylphenol from UK. Many of these data originate from a secondary data source and the validity has not been checked.

- 4-Ethylphenol: Inherently biodegradable
- 2-tert-Butylphenol: Readily biodegradable, meeting the 10 day window criterion
- 3-tert-Butylphenol: Only information available that it "biodegrades in weeks until months"
- 2-sec-Butylphenol: Only information available that it "biodegrades in weeks until months"
- 4-tert-Pentylphenol: Readily biodegradable, not meeting the 10 day window
- 4-tert-Octylphenol: Not readily biodegradable
- Dodecylphenol: Not readily and not inherently biodegradable

Information concerning two other substances was found in the PBT-list number 12 and 13 of the European PBT working group:

- 2,4-di-tert-butylphenol: Not readily biodegradable

- 2,6-di-tert-butylphenol: Not readily biodegradable

However, the substances have now been removed from the lists because they do not fulfil the B and T criteria (PBT sub-group status report, May 2006).

Although QSAR does also not give unambiguous biodegradation results the model predictions tend to predict the substance as not readily biodegradable. Two models (Biowin 1 and 2 from the program package BIOWIN v4.02) predict ptBP to biodegrade fast while Biowin 5 and 6 have "not readily biodegradable" as result. Generally, Biowin 5 and 6 are considered as more valid when predictions of ready versus not ready biodegradation have to be made. Furthermore, when Biowin 1 and 2 predicts a chemichal to be "readily biodegradable" these predictions are less valid than if the same models predicted as substance as "not readily biodegradable". The so called "Danish Datase of QSAR" (http://ecbqsar.jrc.it/), which uses a different training set than those of the BIOWIN models, predicts ptBP as being "not ready biodegradable".

3.1.3.1.3 Degradation in soil

No information on degradation in soil has been submitted.

3.1.3.1.4 Summary of environmental degradation

Concerning biodegradability there are conflicting results available. According to test results from a DOC-Die-Away test ptBP can be regarded as readily biodegradable meeting the 10d window criterion. However, the inoculum in the DOC-Die-Away test might have been adapted to ptBP as it was taken from a predominantly municipal STP from a heavily industrialised area. The results from a Manometric Respirometry Test show that ptBP is ready biodegradable but failing the 10 day window. The monitoring values from different STPs in Austria, which are above the detection limit, support the conservative approach characterising ptBP as readily biodegradable not fulfilling the 10 day window criterion. This implies using a half-life of 50 days in surface water and a half-life of 90 days in soil for the risk assessment. Comparision with other structurally similar alkylphenols does not give a clear picture either. Therefore as a worst case, ptBP is considered as readily biodegradable without meeting the 10 day window.

The atmospheric half-life of ptBP is estimated to 0.4 days.

3.1.3.2 Distribution

The potential environmental distribution of ptBP obtained from a generic fugacity model (Mackay level III) is shown in

Table 3-3. The results show that, if ptBP is released to water or soil, it is unlikely to be distributed into other compartments. If ptBP is released into air, it is likely to be transported to other compartments.

Table 3-3: Environmental distribution of ptBP using a generic fugacity model Mackey level III)

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	39.7 %	0.2 %	0.0 %
Water	23.3 %	95.3 %	0.4 %
Soil	35.9 %	0.2 %	99.6 %
Sediment	1.1 %	4.4 %	0.0 %

The fugacity model indicates a high proportion of ptBP in the air compartment when all ptBP is released to air. This is not entirely realistic as the model does not incorporate degradation processes. In section 3.1.3.1.1 it is estimated that the half life of ptBP in the atmosphere is 0.4 days and would rapidly reduce the amount in the atmosphere. Similar reservations should be applied with respect to levels in soil and water which in part is determined by biodegradation rates.

3.1.3.2.1 Adsorption

No direct information is available. QSAR estimations (Episuite v3.1) give a Koc of 1912. In Freitag (1984) a partition coefficient of 240 in sludge was found and this agrees well with estimated Kp for slugde using a Koc of 1912 and Foc-susp of 0.1 giving Kpsusp=192.

EUSES gives a Koc of 582 based on a Log Kow of 3.29. In the monitoring study of Reinecke (2000) a Koc was measured based on ratio in samples of ptBP in water and suspended matter and amount of TOC in suspended matter. Koc was here measured to 398,000. As this value has not been estimated in a standardised study it should not be used for risk assessment purposes. As there is no valid measured Koc value the EUSES estimated Koc-value of 582 and Kpsusp of 58.2 will be used in this risk assessment.

Experimental data and calculated partition coefficients indicate that ptBP will have a low mobility in soil.

3.1.3.2.2 Precipitation

No direct information is available. Rapid degradation in the atmosphere and relative high water solubility indicates that ptBP, which is released to the atmosphere and not degraded there, will precipitate during rainfall.

3.1.3.2.3 Volatilisation

The volatilisation of ptBP from surface water to air may be estimated by the Henry's Law constant. This is calculated as 0.123 $Pa.m^3 * mol^{-1}$ for ptBP, see section 1.3. The air-water partitioning coefficient ($K_{air\text{-}water}$) may be derived from the Henry's law constant and is calculated as 5.19×10^{-5}. The $K_{air\text{-}water}$ and Henry's law constant are low suggesting that volatilisation is unlikely to be a significant removal mechanism for ptBP from water systems.

3.1.3.2.4 Distribution in wastewater treatment plants

Using the TGD tables and applying the agreed properties for ptBP will give the following distribution in a STP calculated in EUSES for ptBP considered readily biodegradable not fulfilling the 10 d window (values in parenthesis assume that ptBP is fulfilling the 10d window for biodegradation, which is not used in the RAR).

Table 3-4: Simple Treat results for ptBP

Compartment	% of ptBP
Air	0 (0)
Sludge	6 (5)
Biodegraded	63 (83)
Water (effluent)	31 (12)

The results of the report by Scharf & Sattelberger (1999b) have not been used to calculate the concentraion of p-tert-butylphenol after passing a STP in cases where no site specific data has been available because they do not give a clear picture. Several of them are greater-than values and the others, where the concentrations in the outflows were not below the detection limit, show removal rates between 3 and 53. Therefore no mean removal rate has been calculated from these measurements (see chapter 3.1.3.1.2). Instead p-tert-butylphenol is considered readily biodegradable, failing the 10 day window.

3.1.3.3 Accumulation and metabolism

BCF for fish can be predicted from the relationship between Kow and BCF. For substances with a log Kow of 2-6 the following linear relationship can be used according to TGD:

$$\log BCF_{fish} = 0.85 \times \log Kow - 0.70 \text{ (Veith et al. 1979).}$$

The Log Kow of ptBP is 3.29, resulting in a calculated BCFfish of 125, indicating a potential for bioconcentration. No data from a bioconcentration study following OECD guideline 305 is available.
According to Miti (1992) a BCF of 20-43 was achieved in *Cyprinus carpio* exposed to 40 µg/l of PtBP for 8 weeks in a flow through system. When the same test system was run with 4 µg/l a BCF of 48-88 was measured.

The Algae *Chlorella fusca* was exposed to 50 µg/l of ^{14}C-labelled PtBP and after 24h a BCF in algae of 34 was measured.

Freitag et al (1984) studied the BCF in *Leucicus idus melanotus* (using ^{14}C-phenol labelled ptBP). Exposure concentration was measured and found to be 46 µg/l, exposure period was 3 d in a static system. A BCF of 120 was measured. The BCF_{fish} of 120 is comparable to the estimated $BCF_{fish.}$

As a worst case value a BCF of 120 will be used in EUSES.

For the assessment of the bioaccumulation potential of a substance not only the lipophilicity but also the biotransformation and subsequent elimination from the organism has to be taken into account as well. Phenolic materials are rapidly glucuronidated and/or sulphated followed by excretion via the urine or faeces. The principal metabolic pathways are not only available in mammalian organisms, but also in aquatic organisms (e. g. fish; see section 4.1.2.1.1 with respect to studies on metabolism in mammals). It is therefore concluded that available data indicate that ptBP is unlikely to bioaccumulate in the food chain.

3.1.4 Aquatic compartment (incl. sediment)

As indicated in section 3.1.3.2 and 3.1.3.2.4, ptBP will mainly appear and end up in the aquatic compartment.

3.1.4.1 Calculation of predicted environmental concentrations (PEC_{local})

Table 3-5 gives a summary of the local releases to the hydrosphere and local aquatic concentrations. The calculation of these values has been presented in chapter 3.1.2. The regional PEC surface water was determined based on the regional release as given in Table 3-12 and estimated by EUSES to be 0.095 µg/l. The regional PEC includes releases to surface water estimated from site specific data. The regional PEC value is added to the Clocal values estimated in chapter 3.1.2 in order to derive the local PEC values. The regional PEC_{marine} is 0.009 µg/l.

$PEC_{local(water)} = Clocal_{water} + PEC_{regional(water)}$

$PEC_{local(water),ann} = Clocal_{water,ann} + PEC_{regional\ (water)}$

Table 3-5: local release to the hydrosphere

		Release to WWTP/site/d	Release to Surface Water/site/d	Calculated local concentration aquatic	Remark
Production site A		0	0	0	Site spec data avail.
Production site B		1.0 kg/d (actual data)	310 g/d	0.02 µg/l	Site spec data avail.
Production site C		0 (incineration)	0	0	Site spec data avail.
Formulation of ptBP	Not applicable for ptBP				
Processing of ptBP					
Production of Polycarbonates	Monitoring data for all 3 sites available, covering 100% of ptBP used for polycarbonate production				
Site A		0.6 kg/d	122 g/d	0.0063 µg/L	Site spec data avail.
Site B		< 2.9 kg/d	< 58 g/d	< 0.0067 µg/l	Site spec data avail.
Site C			6.2 g/d	0.00024 µg/l	Site spec data avail.
Production of phenolic resins Site specific, site 4 Site specific; site 8, marine		5.5 g/d	1.71 g/d	0.56 µg/l < 0.01 µg/l	Site spec data avail.
Production of Phenolic Resins – generic scenario	Data are available for several phenolic resin production sites; since not all ptBP used for phenol/formaldehyde resin production covered, a generic release estimation based on worst case assumption has been performed				
generic		11.5 kg/d	3.57 kg/d	178 µg/l	Partly adjusted TGD calculations.
Production of epoxy resins Sub-scenario 1 Sub-scenario 2+3 Sub-scenario 4		50 kg/d 125 g/d 125 kg/d	15.5 kg/d 38.8 g/d 38.8 kg/d	775 µg/l 1.94 µg/l 194 µg/l	Partly adjusted TGD calculations
Hydrogenation		0	0	0	Site spec data avail.
Production of Oilfield chemicals	PtBP only in resin which is further chemically reacted, negligible release is expected				
Private use	Negligible				
disposal	Leaching of ptBP from products placed in landfill, estimates release from polycarbonate is 370 g/year= 1.2 g/d				

3.1.4.1.1 Calculation of PEClocal for production

These values are included in Table 3-6 in chapter 3.1.4.1.3.

3.1.4.1.2 Calculation of PEC_{local} for formulation

Formulation is not a relevant step with regard to ptBP.

3.1.4.1.3 Calculation of PEC_{local} for industrial/professional use

A summary of estimated PECs for the aquatic compartment is shown in Table 3-6. When site specific information is used to establish the PECs the highest PEC estimated for each use category is used. When no site specific information is available, estimated PEC values are calculated with EUSES according to the TGD. A regional PECsurface water of 0.095 µg/l is added to Clocal to give the local PECs aquatic. The regional PEC_{marine} is 0.009 µg/l.

Table 3-6: estimated local PECs for the aquatic/marine compartment

Use category	Estimation method	PECaquatic/marine [µg/l]
Production	Site specific, site B	0.11
Phenolic resins	Site specific, site 4	0.66
	Site specific, site 8; marine	< 0.02
Phenolic resins	TGD	178
Polycarbonate resins	Site specific, site A	0.10
Epoxy resins	TGD	
Sub-scenario 1		775
Sub-scenario 2+3		1.94
Sub-scenario 4		194
Regional PEC	TGD	0.095
Regional PEC_{marine}	TGD	0.009
Continental PEC	TGD	0.003

3.1.4.1.4 Calculation of PEC_{local} during life-time service

Release due to private use is assumed to be negligible and no PECs have been estimated.

3.1.4.1.5 Calculation of PEC_{local} for disposal

In section 3.1.2.6 release from landfilled waste from the polycarbonate products was estimated. The amounts were found to be negligible and no further estimations of local concentration or PEC were performed.

3.1.4.1.6 Estimated PEC in STP

In Table 3-7 the highest observed concentrations estimated for the effluent of a STP (= PECstp) are presented for each use category that has an emission to waste water. Only the highest values estimated are presented for each use category, respectively.

Table 3-7: estimated local PECs for the STP compartment

Use category	Estimation method	PEC_{STP} mg/l
Production (site B)	Site specific	0.02
Phenolic resins	Site specific (water monitoring program)	≈ 0.01
Phenolic resins	Site specific (site 8, LOD)	0.01
Phenolic resins	TGD generic scenario	1.78
Polycarbonate resins	Site specific, location A	0.0013
Epoxy resins Sub-scenario 1 Sub-scenario 2+3 Sub-scenario 4	TGD – generic scenarios	 7.75 0.02 1.94

3.1.4.2 Measured levels

Monitoring values are few and some values may be outdated.

Table 3-8: Monitoring values for surface water

Site	ptBP in water [µg/l]	Reference
Austria, 34 samples	0.039, 1 with detectable conc.	Scharf & Sattelberger, 1999a
Germany, Elbe and tributaries	0.0014-0.078, 14 samples mean 0.0081 median 0.0021	Reinecke, 2000
Germany, Weissen Elster	0.001-0.0053, 6 samples	Reinecke, 2000
Germany, Elbe and estuary	0.0-0.043, 19 samples mean 0.0051	Reinecke, 2000
Germany, Elbe at STP outflow site	0.0013-0.0021, 2 samples	Reinecke, 2000
Germany, Rhein	Identified in 5 of 16 samples	Kunte et al, 1975
USA, infiltration water from waste site	0.035-0.118	Tomson et al., 1981
USA, River receiving industrial chemical plant waste water	3, 1 sample; of heavily contaminated site	Jungclaus et al., 1978

Table 3-9: Monitoring values related to suspended matter and sludge

Site	ptBP [µg/kg]	Reference
Sweden, 2 municipal STPs sludge concentration	1.9-2.6 4 dwt, 4 samples	Hajslova, 2002
Germany, Elbe and tributaries, suspended matter	23-93, 11 dwt, 11 samples mean 46	Reinecke, 2000
Germany, Schnackenburg Feb-July 1998, suspended matter	19-81, 6 dwt, 12 samples mean 53	Reinecke, 2000
USA, river at WWTP of chemical plant	200-7000 dwt, 5 samples, of heavily contaminated site	Jungclaus et al., 1978

Table 3-10: Monitoring values related to waste water treatment sites

Site	ptBP in water [µg/l]	Reference
Austria, 15 STP, inflow concentration	0.063-0.887, mean 0.212, 14 samples with detection	Scharf & Sattelberger, 1999b
Austria, 17 STP, outflow concentration	<0.05-0.448, mean 0.094 9 samples with detection	Scharf & Sattelberger, 1999b
Sweden, 2 municipal STP inflow concentration	0.046-0.098, 4 samples	Hajslova, 2002
Sweden, 2 municipal STP outflow concentration	0.052-0.059, 4 samples	Hajslova, 2002
Germany industrial STP	0.388-0.808, 2 sites	Reinecke, 2000
Germany municipal STP	0.0086-0.033, 3 sites	Reinecke, 2000
USA, STP, outfow of chemical plant	1-75, 4 samples of heavily contaminated site	Jungclaus et al., 1978

3.1.4.3 Comparison between predicted and measured levels for surface water

The regional PEC for surface water estimated by EUSES is 0.095µg/l. The highest observed measured value in Europe is 0.078 µg/l. Measured concentrations in surface water (Table 3-8) are therefore below the PECregional. This indicates that the estimated regional $PEC_{surface\ water}$ does not underestimate surface water concentrations. Measured samples are mostly taken from rather large water systems, and it may therefore be assumed that these measurements do not represent typical local situations.

There are no monitoring data that can be assigned to a specific life cycle stage or a local use site. The risk assessments for local sites will be performed using the estimated $PEC_{surfacewater}$ in Table 3-6.

Monitoring values for sediment are missing and it was not considered appropriate to calculate a PEC sediment using the equilibrium partitioning method.

3.1.5 Terrestrial compartment

According to EUSES 6 % of ptBP directed to the STP will end up in the sludge of a STP. EUSES estimates a concentration in agricultural soil assuming a sludge deposition rate of 0.5 $kg \cdot m^{-2} \cdot year^{-1}$. The estimated PEC values in agricultural soil are shown in Table 3-11. Only the generic scenarios for phenolic and epoxy resins result in a PEC for agricultural soil. The regional PEC for agricultural soil as estimated by EUSES is 0.04 µg/kg wwt.

Table 3-11: Estimated PEC_{soil} for scenarios estimated according to TGD default assessment.

Use category	Estimation method	PEC agricultural soil [µg/kg wwt]
Phenolic resins	TGD	1,110
Epoxy resins	TGD	
Sub-scenario 1		4,830
Sub-scenario 2+3		20
Sub-scenario 4		1,210

Summing up all releases to industrial soil according to the default release fractions given in the TGD for the use category "epoxy resins" gives a total regional emission to soil of 0.10 kg/d in the regional compartment and 0.11 kg/d in the continental compartment. As shown in chapter 3.1.3.2.1 adsorption of ptBP is assumed to be high in soil and it is therefore not expected that ptBP from soil will migrate to groundwater. With a half life of 90 d in soil there does not seem to be any risk of accumulation of ptBP in soil over time, but there may be significant ptBP concentrations in soil after sludge application.

3.1.6 Atmosphere

For all use categories without site specific information, release to air has been estimated using TGD default values. These emissions are summarised in Table 3-12. The total regional emission is 41.9 kg/d and for the continental compartment the total is 123 kg/d. This is, however, dominated by the default emissions for epoxy resins in sub-scenario 2 and 3. The estimated emission to air is much higher than estimated for the aquatic compartment. MacKay level III fugacity distribution indicates that 39 % is present in the air compartment when release is only to air (chapter 3.1.3.2). However, the fugacity estimation does not include degradation processes. In section 3.1.3.1.1 it is estimated that the half life of ptBP in the atmosphere is 0.4 days or less. EUSES estimates a regional PEC air of 0.75 ng/m^3. With a half life of less than a day, no build up in the atmosphere is expected and no further assessment of the air compartment is thought necessary.

Sub-scenarios 2 and 3 of epoxy resins are the major contributors to the release of ptBP into the air compartment. The local PECair for this use is 5.71 $\mu g/m^3$.

3.1.7 Secondary poisoning

According to data presented in section 3.1.3.3, ptBP is unlikely to bioconcentrate in the food chain. Further assessment of exposure through the food chain is therefore not warranted.

3.1.8 Calculation of PECregional and PECcontinental

Using data from Table 3-5 (local releases to the hydrosphere) and TGD estimates as calculated by EUSES, the daily release has been estimated for all life cycle stages and results are presented in.Table 3-12. The regional release is set to local release when the local site uses more than 10 % of the total volume for this use category. However, as the releases [kg/d] as presented in Table 3-12 are on an annual basis (365 days per year) they are in some cases lower than the local releases (see Table 3-5) which are estimated using the number of working days per year, a figure which usually is lower than 365 days.
The regional aquatic $PEC_{surfacewater}$ is 0.095 µg/l

The regional atmospheric PEC_{air} is 0.75 ng/m^3

Table 3-12: Summary of regional and continental releases to wwtp and air

	Regional [kg/d]		Continental [kg/d]	
	air	**Wwtp**	**air**	**Wwtp**
I Production (site specific)	0.77	0.269*	0	0.0*
II Distribution (negligible)				
III Phenolic resins (TGD)	0.041	9.45	0.37	31.6
III Polycarbonates (site specific)		0.186*	0	0
III Epoxy resins (TGD)				
Sub-scenario 1	0	11	0	11
Sub-scenario 2+3	41.1	0.027	123	0.08
Sub-scenario 4	0	2.05	0	2.05
III Hydrogenation (site specific)	0	0	0	0
III Oilfield chemicals (negligible?)	0	0	0	0
SUM	41.9	23.0	123	44.7

*direct release to surface water

The regional PECsurface water is estimated by EUSES to 0.095 µg/l and the continental PECsurface water is 0.003µg/l. The regional marine PEC is 0.009 µg/l

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)

Effects studies are only available for the aquatic compartment. Based on present information available for ptBP with respect to its use and chemical properties other compartments seem not at risk. Therefore no further information is needed with respect to effects for these compartments.

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity test results

Several studies are available for the aquatic compartment. The acute toxicity test results relevant for the aquatic compartment are listed in Table 3-13, Table 3-15 and Table 3-16.

3.2.1.1.1 Fish

Table 3-13: Acute toxicity to fish

Test species	Test method (test period hours)	Quality	Result LC50/EC50 [mg/l]	Reference
Pimephales promelas	Other 96 hours	Valid	5.1 (M)	Holcombe et al., 1984
Oryzias latipes	OECD 203 96 hours	Valid	5.1 (N)	EA of JAPAN, 1996
Oryzias latipes	JISK 0102-1986-71 48 hours	Not valid	4.0 (N)	Miti, 1992
Rainbow trout	Other 96 hours	Not valid	>1 (N)	SafePharm Laboratories Ltd., 1991

M: measured concentrations

N: nominal concentrations

Acute toxicity

The toxicity to fish has been assessed in several studies.

In a flow-through test with fathead minnow (*Pimephales promelas*) a 96h-LC50 of 5.14 mg/l (4.7-5.6 mg/l) was determined based on measured concentrations (Holcombe et al., 1984). No test guidelines were followed; however, the test was performed in a US EPA lab and is considered valid as it is assumed that US EPA standards had been followed. The purity of ptBP was 99 %. There were 5 test concentrations; measured mean concentrations were 1.16, 1.87, 3.1, 5.44 and 9.47 mg/l, giving a mean recovery of 99%. PtBP was tested as one of 24 organic compounds and specific test conditions for the test with ptBP are not available. The following parameters are reported for the whole study: The test temperature was 24.6±1.4°C,

oxygen levels were in the range of 4.6 to 8.8 mg O_2/l and the pH was in the range of 6.9 to 7.7. The oxygen level of 4.6 mg O_2/l would be below the 60% oxygen saturation required for a valid test. Test water was taken form Lake Superior and the mean hardness was 44.9 mg/l. The alkalinity was 42.9 mg/l. The flow-through system gave 16 water volume exchanges per day. The test is considered to be valid.

In a study using *Oryzias latipes* according to OECD 203 a 96 h-LC50 of 5.1 mg/l was determined. DMSO was used as a solubilizer. The study is a semi static study based on nominal concentrations.

In a study using *Oryzias latipes* according to the Japanese standard JISK 0102-1986-71 a 48 h-LC50 of 4.0 mg/l was determined. The study is a semi static study based on nominal concentrations. The study is not considered valid because of non standard test period.

In an acute toxicity study with rainbow trout with an exposure period of 96 hours no toxicity was observed up to the highest concentration that could be prepared due to the limited solubility under the test conditions (corresponding to 1 mg/l) (SafePharm,1991). The test is not considered valid.

Other studies cited in the literature are of poor quality and/or no details have been reported.

3.2.1.1.2 Endocrine disruption in fish

Concern has been raised to whether ptBP has endocrine disrupting properties. Endocrine disruption is defined as
1) **"…**an exogenous substance that causes adverse health effects in an intact organisms or its progeny through alterations in the function of the endocrine system…" (TGD, 2003).
2) "…exogenous agents that interfere with the production, release, transport, metabolism, binding and action or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and regulation of developmental process…" (EPA, 1996)**.**

The chemical ptBP belongs to a group of chemicals collectively known as alkylphenols. Recently focus has been directed to the estrogenic properties of these chemicals. Para-substituted tertiary octylphenol (ptOP) and nonylphenol (NP) have been shown to display estrogenic properties in various *in vitro* as well as *in vivo* studies (Jobling and Sumpter, 1993; Jobling *et al.,* 1996; Knudsen *et al*., 1998; Anersen et al., 1999; Gronen *et al.,* 1999; Knudsen and Pottinger, 1999; Tollefsen *et al*., 2002; Tollefsen *et al*., 2003). Even though their estrogenic potency is more than 1000 times less potent than the natural estrogen 17β-estradiol, these chemicals are among the most potent estrogenic industrial chemicals found in the environment. Although there is a wealth of experimental data on OP and NP which demonstrate that these chemicals are estrogenic *in vivo*, little reliable in vivo data is available for ptBP. There is, however, substantial data on the in vitro potency of this chemical. These studies include use of recombinant cell reporter systems which express the estrogen receptor (Yeast estrogen screen), use of the estrogen dependable MCF_7 cancer cells and cultivated native liver cells from fish displaying estrogenic biomarkers of effect (vitellogenin induction). Results from these studies show that ptBP is able to induce an estrogenic response in screening assays derived from both human cells and fish. In the yeast estrogen screen, which is stably transfected with the human ER, ptBP is weakly estrogenic with a relative potency of about one million compared to 17β-estradiol (Routledge and Sumpter, 1997). The relative

potency of ptOP was roughly 100 times higher than ptBP. In these studies, para-substituted alkylphenols with an alkyl chain length longer than three methyl groups were able to induce estrogenic effects and the estrogenicity of butylphenol was not dependent on the shape of the alkyl group (i.e. whether it was tertiary or secondary). Other studies using the estrogen dependent MCF7 cancer cell line, which also express the human ER, seems to confirm the studies performed on yeast estrogen screen (Soto *et al*., 1995; Körner *et al*., 1999). In these studies, ptBP has a relative potency of about 200-300 000 times lower than 17β-estradiol and 20 to 100 times lower than ptOP. Interestingly, the relative estrogenic potency of ptBP seems to be considerably higher in screening systems utilising the fish ER. Jobling and Sumpter (1993) presented data on the alkylphenol induced production of vitellogenin, an estrogenic biomarker, in liver cells from rainbow trout. In their study, ptBP was about 10 000 times less potent than 17β-estradiol and more potent than ptOP. Binding of a range of n-alkylphenols to the fish and human ER seems to support that the mid-sized alkylphenols (butyl and pentylphenol) have higher relative affinity to the fish than the human ER (Knudsen and Pottinger, 1999; Tabira *et al*., 1999). An ongoing study performing an interspecies comparison between the human and fish ER with regard to ER binding and receptor activation (estrogenic response) seems to confirm that ptBP is not only estrogenic, but that fish may be more susceptible to this chemical than humans (Olsen *et al*., 2003). On the basis of these studies it may be safe to state that ptBP is weakly estrogenic.

Whether the estrogenic properties may lead to adverse effects through endocrine disruption may only be answered by conducting thorough *in vivo* studies with endocrine related endpoints. We have found that the in vitro estrogenic properties of ptBP to be comparable to ptOP and Bisphenol A in terms of affinity to the rainbow trout ER and the estrogenic potency in a fish *in vitro* screening assay (Tollefsen, personal communication) In several studies with Bisphenol A (BPA) and ptOP (see RAR for BPA and ptOP) NOECs for reproductive effects have been proposed to be set at 16 and 12 μg/l, respectively.
4-tert-pentylphenol (ptPP) is a closely related chemical that has been extensively studied with respect to endocrine disrupting effects.
A recent risk assessment report on para-tert-pentylphenol (ptPP), Draft August 2006, is supplying some data that may facilitate the risk assessment of ptBP. The in vivo endocrine disrupting effects of ptPP has been reported in several studies (Gimeno et al., 1996; Gimeno et al., 1997; Gimeno et al., 1998; Gimeno et al., 1998; Hagino et al., 2001; Panter et al., 2002; Seki et al., 2003; Panter et al., 2006), where most NOECs of individual endpoints have been reported in the 1-250 ug/l range. Table 3-14 : Toxicity of 4-tert-pentylphenol to freshwater fish (AED = Australasian Ecotoxicity Database; KC = Klimisch code). is a copy of table 4.1 in the UK RAR for ptPP and depict the different NOECs reported. Details about the different studies are provided in the risk assessment report and the original documents. As can be seen from the reported studies on ptPP, the lowest NOEC were found for testis differentiation/histology (Gimeno et al., 1998; Gimeno et al., 1998), male secondary sex characteristics (Hagino et al., 2001) and vitellogenin induction (Gimeno et al., 1998; Panter et al., 2002; Seki et al., 2003; Panter et al., 2006) at low ug/l concentrations. Effects on gonadosomatic index (NOEC <32) has also been reported in common carp (Gimeno et al., 1998) whereas male secondary sex characteristics were affected at as low as 1 ug/l concentrations (Hagino et al., 2001). In the risk assessment of ptPP a NOEC of 100 ug/l (endpoints abnormal sex differentiation, sex ratio and reproductive impairment) has been proposed, based on the fish full life-cycle test on Medaka (Seki et al., 2003) since this was the study of longest duration and considered to be the best performed study from those available. However, effects were also seen at lower concentrations in other studies (a.o. Gimeno et al. 1997, 1998a, 1998b), but were not considered to give sufficient information to derive a

PNEC. The possibility that effects on endocrine related endpoints may occur at lower concentrations was therefore recognised and these results were taken into account when applying an assessment factor.

Table 3-14 : Toxicity of 4-tert-pentylphenol to freshwater fish (AED = Australasian Ecotoxicity Database; KC = Klimisch code).

Species	Chemical tested	Age/ size	Static/Flow-through	Temp. (°C)	Dissolved oxygen (mg l^{-1})	Hardness (mg $CaCO_3$ l^{-1}) or salinity (‰)	pH	Endpoint	Concentration (mg l^{-1})	Reference	Validity scores
Freshwater – chronic											
Oryzias latipes (medaka)	4-*tert*-pentylphenol (99.7% purity)	Two generations (101-d F_0, 61-d F_1), starting with fertilised eggs	Flow through	24	Not stated	44 - 61	7.2-7.6	F_0 60-d survival & growth NOEC	0.402	(Seki *et al.*, 2003)	AED: High KC: 1
								F_0 abnormal sex differentiation NOEC	0.1		
								F_0 vitellogenin induction NOEC	<0.0511		
								F_0 reproductive impairment NOEC	0.1		
								F_1 length NOEC	0.1		
								F_1 sex ratio NOEC	0.1		
Oryzias latipes (medaka)	4-*tert*-pentylphenol (purity not stated)	Newly hatched	Flow through	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)	AED: High KC: 2
								Dorsal fin length	0.01		

Species	Chemical tested	Age/ size	Static/Flow-through	Temp. (°C)	Dissolved oxygen (mg l^{-1})	Hardness (mg $CaCO_3$ l^{-1}) or salinity (‰)	pH	Endpoint	Concentration (mg l^{-1})	Reference	Validity scores
								Anal fin length	0.01		
								Papillary processes on anal fin	0.001		
								Differentiation of male testes into ovaries	0.001		
Oryzias latipes (medaka)	4-*tert*-pentylphenol (99.7% purity)	Eggs to 60 days posthatch	Flow through	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 60d posthatch	≥ 0.238	(Yokota *et al.*, 2005)	AED: High KC: 1
Cyprinus carpio (common carp)	4-*tert*-pentylphenol (purity not stated()	50-day-old fish	Intermittent flow-through	Not stated	Not stated	Not stated	Not stated	Percentage oviduct NOEC	0.1	(Gimeno *et al.*, 1996)	AED: Acceptable KC: 2
								Number of primordial germ cells NOEC	0.32		
Cyprinus carpio (common carp)	4-*tert*-pentylphenol (>99% purity)	Fertilised eggs, yolk sac larvae, larvae, or fingerlings of a genetically	Semi-static	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	≥ 0.14	(Gimeno *et al.*, 1997)	AED: Acceptable KC: 2

Species	Chemical tested	Age/ size	Static/Flow-through	Temp. (°C)	Dissolved oxygen (mg l^{-1})	Hardness (mg $CaCO_3$ l^{-1}) or salinity (‰)	pH	Endpoint	Concentration (mg l^{-1})	Reference	Validity scores
		male population									
Cyprinus carpio (common carp)	4-*tert*-pentylphenol (>99% purity)	210 days posthatch (22 ± 0.44 g)	Flow-through	25 ± 1	>6	Not stated	7.6 ± 0.2	90 d NOECs:		(Gimeno *et al.*, 1998)	AED: High KC: 2
								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		
Cyprinus carpio (common carp)	4-*tert*-pentylphenol (>99% purity)	50 days posthatch (1.3-1.7 g)	Flow-through (intermittent)	25 ± 0.8	4-8	210	7.6 ± 0.4	Growth NOEC	>0.256	(Gimeno *et al.*, 1998)	AED: High KC: 1
								Reproductive tract development	<0.036		
								Primordial germ cell	<0.036		

Species	Chemical tested	Age/ size	Static/Flow-through	Temp. (°C)	Dissolved oxygen (mg l^{-1})	Hardness (mg $CaCO_3$ l^{-1}) or salinity (‰)	pH	Endpoint	Concentration (mg l^{-1})	Reference	Validity scores
								NOEC			
								Vitellogenin induction NOEC	0.09		
Cyprinus carpio (common carp)	4-*tert*-pentylphenol (99% purity)	Cultured hepatocytes	Semi-static	24	No	Not stated	No	96-h vitellogenin induction NOEC	3.285	(Smeets *et al.*, 1999)	AED: Acceptable KC: 2
Pimephales promelas (fathead minnow)	4-*tert*-pentylphenol (>98% purity)	Embryos (24-h post-fertilisation)	Flow-through	25 ± 1	>70% ASV	≥ 200	7.5 ± 0.5	Larval survival NOEC	0.56	(Panter *et al.*, 2006)	AED: High KC: 1
								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		

Extended early lifestage pilot fish study with fathead minnow (Pimephales promelas)

The close resemblance of ptBP with ptPP strongly suggested performing an Extended Early Life Stage test on fish in order to document levels for any adverse endocrine disrupting effects in vivo. A non GLP pilot study with ptBP to determine test concentrations and evaluate potential endocrine endpoints to be used in a partial life cycle test with fathead minnow (Pimephales promelas) has been performed with 4-tert-butylphenol at nominal concentrations of 1, 30, 100 and 500 ug/L (measured cocentrations: 2, 25, 82, 413 ug/l). The protocol was based upon the experimental design presented in ANNEX E, Partial Life Cycle Test (or Extended Early Life-Stage Test) of the OECD "Detailed Review Paper on Fish Screening Assays for the Detection of Endocrine Active Substances (October 2004) . The study also incorporated procedures in the OECD Guideline for Testing of Chemicals, 210: Fish Early-Life Stage Toxicity Test and ASTM Standard E1241-88 Standard Guide for Conducting Early Life StageToxicity Tests with Fish. Main findings of the pilot study were as follows (nominal concentrations in brackets):

1. **Water concentrations:** measured water concentrations were (2, 25, 82, 413 ug/l) deviated from the nominal concentrations (1, 30, 100, 500 ug/l).
2. **Hatching success:** No effects were observed in the hatching success in any group, but a significant delay in hatching for the 82 /l (100 ug/l) and 413 ug/l (500 ug/l) group was observed. Although the biological significance of these findings was questioned, a need for improved sampling design was proposed to properly assess this effect.
3. **Survival of Larvae and Juvenile fish:** No significant differences in survival of fish at any fish stage observed.
4. **Sex ratio:** A significant reduction in male fish and fish displaying male gonads was observed at the 413 ug/l (500 ug/l) group based on gross internal sex and on external sex determination.
5. **Growth:** No significant changes in length and weight of females were observed. A treatment related effect on fish length and weight were observed for males at the concentration of 413 ug/l (500 ug/l).
6. **Gonadosomatic index (GSI):** No significant changes in GSI of either males or females were observed.
7. **Vitellogenin (Vtg):** No significant changes in Vtg in males were observed due to high inter-replicate variations. No significant changes observed in females, although it is proposed that the elevated levels of Vtg in the 423 ug/l (500 ug/l) group was a treatment-related effect. Large intra and inter-replicate variation was clearly evident in both males and female groups, and was especially evident in male data due to high number of samples below the level of quantification (LOQ ≈ 590 ng/ml). After reviewing the test report, some Member States expressed a concern at TCNES IV-06 about a trend in reduction of Vtg in females at the 2 ug/L (1 ug/L) and 25 ug/L (30 ug/L) exposure groups. The observed trend in Vtg was not reported by the contract laboratory to be significant by using the current experimental design. No clear biological (endocrine) mechanism to explain the results has been presented. A

decrease of Vtg levels at low concentrations and an increase at high levels would be difficult to explain on a mechanistic basis. However, effects due to unknown mechanisms of action could not be completely disregarded. Vitellogenin synthesis in fish is widely considered to be a reliable and sensitive indicator of exposure to estrogenic chemicals, although the ecological significance is not yet known. In light of the ongoing OECD process foccussed on the use and interpretation of this biomarker and the lack of sufficient statistical data from the PILOT study, it would be advisable to provide more data in order to rule out the indicated trend in Vtg in females at low doses.

8. **Onset of male sex characteristics:** A treatment related effect on fish displaying at least one male secondary sex characteristic was observed in the 413 ug/l (500 ug/l) group. It was not possible to discriminate whether the observed effect were due to a delay in maturation or lack of ability to develop male secondary sexual characteristics.

9. **Pigmentation on dorsal fin or nose/lip:** Pigmentation on the dorsal fin or nose/lip of fish in the treatment groups was not significantly different from the control, although a treatment-related effect was observed at the 413 ug/l (500 ug/l) concentration.

10. **Presence of fatpad and fatpad Score**: A significant effect was observed on the reduction of fatpad/fatpad score in males of the 413 ug/l (500 ug/l) treatment group. The male fish in the 82 ug/l (100ug/l) treatment displayed a treatment related effect, although this change was not statistically significant using the current experimental design.

11. **Presence of Tubercles, Tubercle Count and Tubercle Score**: Presence of tubercles (counts and score) of fish in the treatment groups were not significantly different from the control, although a treatment-related effect was observed at the 413 ug/l (500 ug/l) concentration.

12. **Histopathology:** feminization of gonadal ducts was occurring in males at 413 ug/l (500 ug/l), and presence of oocytes in male testes (intersex). The presence of intravascular fluid in female ovaries, which was indicated to be caused by increased

It can be concluded that the most sensitive endpoints observed in the PILOT study was delayed hatching, presence of intravascular fluid in female gonads and the presence of fatpads and fadpad score in male fish. The study thus suggests a NOEC of 25 ug/l (30 ug/l) and a LOEC of 82 ug/l (100 ug/l). A negative trend in Vtg production in females was indicated at even lower concentrations. The number of samples was few so the statistical significance of this could not be established, however a clear biological (endocrine) mechanism to explain the results has not been presented.

The current design of the PILOT study does not allow for the statistical power required for the final test. This applies in particular to the number of fish analysed for gonad histology and vitellogenin. In terms of the data used for gonad histology, OECD DRP suggests conclusions to be made upon 40 fish, whereas the present test has utilised 3 males and 3 females from each replicate (12 males and 12 females per treatment). Since males and females need to be treated as separate groups during the statistical treatment, the total number of fish is only about one third of that recommended.
The lack of proper statistical data also applies for the analysis of vitellogenin, where OECD DRP suggest the use of data from 20 fish per treatment, and the pilot study has obtained data

from 3 males and 3 females from each of 4 replicas (totally 12 males and 12 females per treatment). As for gonad histology, males and females need to be statistically treated as independent groups, and the current design of the PILOT study does thus provide only about half of the number of fish recommended. The large variability is clearly illustrated in the apparent (non-significant) lower Vtg values in females in the two lowest concentration group, where increase in sample numbers would have increase confidence in the results. In addition to this, the analytical method for vitellogenin was hampered by high numbers of samples that were below the quantification limit due to low sensitivity of the method used. The LOQ was about 1/50 times higher than that reported for other commercially available ELISAs (Eidem et al., 2006). The lack of effects seen in males may thus be caused by lack of ability to analyse Vtg in these samples, and not that effects were not present. Since male fish is considered to be more sensitive than females to environmental estrogens, effects should be expected at lower concentrations in a final study using a more appropriate study design.
The concentration range chosen (nominal: 1, 30, 100, 500, measured: 2, 25, 82, 413 ug/l) is intended to cover a broad concentration range and thus is not optimized to the concentrations that may cause effects. This is clearly evident in the higher end of the concentration range where a dilution factor of about 5 is used (e.g. 100 and 500 ug/l group). According to OECD DRP guidelines, the dilution factor should not exceed 3.2 and current study design is thus not optimal for providing data in the range where some of the effects were occurring.

In essence, the rapporteur considers the present study and results of the study as valuable information to optimize and improve the experimental design of the planned final study. The present PILOT test has shortcomings because the current design does not allow for the statistical power required and the PILOT test does not fulfil the test criteria proposed by the OECD draft guideline (OECD, 2004) and recent recommendations by the WMG eco working groups (WMG-Eco, 2004).

Conclusion and predicted No-effect Concentration (PNEC)

The main results of the PILOT study with ptBP was that the most sensitive endpoints were delayed hatching, presence of intravascular fluid in female gonads and the presence of fatpads and fadpad score in male fish. The PILOT study provides data for supporting a NOEC of 25 ug/l (30 ug/l) and a LOEC of 82 ug/l (100 ug/l). The provisional NOEC could be supported by reading across to data on p-tert-pentylphenol, however there were concerns about a potential reduction of vitellogenin (Vtg) levels in females at low concentrations as indicated by the data from the pilot study. There is concern that even if read-across to the available data on p-tert-pentylphenol may be appropriate for certain EDC mediated mechanisms such as feminization of males, there is a large uncertainty related to whether potential effects on female reproductive parameters will be covered by read-across to p-tert-pentylphenol based on the data presently available.

The level of uncertainty in the present approach of read-across was proposed to bee too high to abandon the definitive extended ELS fish study. The majority of the MS agreed that the definitive long term fish test should be conducted in accordance with the OJ requirements.

3.2.1.1.3 Aquatic invertebrates

Table 3-15: Toxicity to invertebrates

Test species	Test method (test period hours)	Quality	Result LC50/ EC50 [mg/l]	Reference
Daphnia magna	OECD 202 (48 hours)	Valid	6.7 (N)	EA of JAPAN (1996)
Daphnia magna	Din 38412 (48 hours)	Valid	3.9 (N)	Kuhn et al., 1989
Daphnia magna	OECD 202, GLP (48 hours)	Valid	4.8 (N) 3.2 NOEC	NIVA (2001a)
Crangon septemspinosa	Other (96 hours)	Valid	1.9 (M)	McLeese et al., 1979
Daphnia magna	OECD 202, 21 d reproduction study	Valid	2.0 EC50 0.73 (M) NOEC	EA of JAPAN (1996)

M: measured concentrations

N: nominal concentrations

Acute toxicity

The toxicity of ptBP to invertebrates was assessed in a semi-static test with *Daphnia magna*, according to OECD guideline 202. DMSO was used as a solubilizer. The EC50 (48 hours) was determined to be 6.7 mg/l (5.2 – 9.7 mg/l) (EA of Japan 1996).

In another study with static test conditions using *Daphnia magna* an EC50 (48 hours) of 3.9 mg/l (3.4 – 4.5 mg/l) was determined (Kühn et al., 1989). The test was performed according to the German test standard DIN 38412. Nominal concentrations were used to estimate test endpoints.

The toxicity of ptBP to invertebrates was assessed in a test with *Daphnia magna*, according to OECD guideline 202 and conducted according to GLP (NIVA 2001a). Tested nominal concentrations were 0.56, 1.0, 1.8, 3.2 and 10 mg/l. The EC50 (48 hours) was determined to be 4.8 mg/l. The NOEC in the study was 3.2 mg/l. The purity of the test substance was given to be 99%.

The acute toxicity of ptBP was tested with the marine species *Crangon septemspinosa* (McLeese et al., 1979). A 96 h LC50 of 1.9 mg/l was established. No standard guideline was followed. The LC50 is based on measured concentrations.

Long-term toxicity

In a 21d- reproduction study with *Daphnia magna* according to OECD guideline 202, using semi-static conditions the EC50 (21d, reproduction rate) was determined to be 2.0 mg/l. The NOEC was 0.73 mg/l, and the LOEC was 2.3 mg/l. DMSO was used as a solubilizer (EPA of Japan, 1995)

3.2.1.1.4 Algae

Table 3-16: Toxicity to algae

Test species	Test method (test period hours)	Quality	Result [mg/l]	Reference
Selenastrum capricornutum	OECD 201, GLP (72 hours)	Valid	EC50 = 14 NOEC = 0.32 (N)	NIVA (2001b)
Selenastrum capricornutum	OECD 201 (72 hours)	Valid	EC50 = 22.7 NOEC = 9.53 (M)	Huels AG (1985)

M: measured concentrations

N: nominal concentrations

In a 72h algae toxicity test following OECD guideline 201 with *Selenastrum capricornutum* an EC50 of 22.7 mg/l was identified (Huels, 1985) The NOEC was 9.53 mg/l and the LOEC was found to be 17.2 mg/l. The test was performed under static conditions; biomass inhibition was used as an endpoint. Five different concentrations were used (nominal: 9.53, 17.2, 30.9, 55.6, and 100 mg/l) and the test concentrations were analytically monitored. In addition a solubilizer was used. The purity of the test substance was given to be 99.5%.

In a 72h algae toxicity test following OECD guideline 201 with *Selenastrum capricornutum* an EC50 of 14.0 mg/l (13.4-15.3 mg/l) and a NOEC of 0.32 mg/l was identified (NIVA 2001b). Both results are based on growth rate and on nominal concentrations. The study was performed according to GLP. Tested nominal concentrations were 0.32, 0.56, 1.0, 1.8, 3.2, 5.6, 10 and 18 mg/l. The purity of the test substance was given to be 99%.

3.2.1.1.5 Micro-organisms

In an oxygen consumption test with *Pseudomonas putida* the EC10 was determined to be 140 mg/l (Huels AG, 1994). The exposure period was 6 hours. A 5 % emulsifier concentration (nonylphenol ethoxy propoxylate) was used to obtain sufficient solubility of the material.

The population growth inhibition of *Tetrahymena pyriforms* was investigated in a period between 48-60 h after exposure (Schultz et al. 1986). The study was a static test; no information on the standard is given. An EC50 with respect to growth inhibition of 18.4 mg/l was observed.

In a ready biodegradation test (NIVA, 2003c) results with the toxicity control indicated that biodegradation of aniline was inhibited by 25 mg/l of ptBP. At a concentration of 15 mg/l degradation proceeded satisfactory but with a lag phase.

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

3.2.1.2.1 Surface water including sediment

Acute test data are available for fish, invertebrates and algae, covering 3 different trophic levels. In all of these acute tests the effect levels were found to be in the range of 1.9 – 22.7 mg/l. *Daphnia* is slightly more sensitive compared to fish and algae. In addition, a chronic test for invertebrates (*Daphnia magna*) is available. According to the TGD the algae test can be regarded as a chronic test, since, under technical aspects, it covers several generations. Therefore 2 chronic tests are already available. Since the NOEC includes invertebrates which was the trophic level showing the lowest L(E)C50, the TGD allow reducing the application factor to 50.

The lowest available NOEC is 320 µg/l for *Selenastrum capricornutum*

NOEC 320 µg/l /50 = 6.4 µg/l

$PNEC_{aquatic}$ = 6.4 µg/l

For deriving a $PNEC_{marine}$ an assessment factor of 500 has to be applied to the NOEC for algae because only two long-term NOECs from freshwater or saltwater species representing two trophic levels (algae and crustaceans) are available.

$PNEC_{marine}$=320 µg/l /500 = 0.64 µg/l

No test is available for sediment dwelling organisms. According to the TGD the equilibrium partitioning method may be used to estimate the $PNEC_{sediment}$. However, as no direct measurements of ptBP are available from sediment, PEC concentrations would have to be estimated in the same fashion giving the same PEC/PNEC ratios as for surface water. Therefore a $PNEC_{sediment}$ has not been derived.

3.2.1.2.2 Sewage treatment plant

According to the TGD the tested concentration at which toxicity to the inoculum can be ruled out with sufficient reliability can be considered as a NOEC for the toxicity to micro-organisms of a STP. The test with *Pseudomonas putida* (Hüls AG, 1994) gave an EC10 of 140 mg/l and is therefore less sensitive than the toxicity control in the ready biodegradability test (OECD 301 F; NIVA, 2003c). In this ready biodegradation test results with the toxicity control indicated that biodegradation of aniline was inhibited at 25 mg/l of ptBP. At a concentration of 15 mg/l degradation proceeded satisfactory but with a lag phase. This value should be applied as an EC10 with an assessment factor of 10 giving a

$PNEC_{micro\text{-}organisms}$ of 1.5 mg/l.

3.2.2 Terrestrial compartment

There are no toxicity tests available with respect to the terrestrial compartment. The derivation of the PNEC for the terrestrial compartment must therefore be performed applying the partition equilibrium method of the TGD.

$PNEC_{soil}=K_{soil\text{-}water}/RHO_{soil}*PNEC_{aquatic}*1000$

PNECsoil=19.5 / 1700 * 6.4 * 1000 = 73 µg/kg wwt

3.2.3 Atmosphere

No information is available or needed at this stage due to low exposure of the atmosphere and the short half life of ptBP when released to the atmosphere.

3.2.4 Secondary poisoning

Available data indicate that ptBP is unlikely to bioaccumulate in the food chain. No further information is considered necessary with respect to effects through the food chain.

3.3 RISK CHARACTERISATION[8]

This assessment concludes that the aquatic compartment is the one of main concern with respect to the use of ptBP. The risk characterisation is therefore performed for this compartment. No site specific information on either concentration in sediments or on effects on sediment dwelling organisms is available. In the absence of both these entities, PEC and PNEC would have to be estimated according to the partitioning method giving the same PEC/PNEC ratio as for surface water.

3.3.1 Aquatic compartment (incl. sediment)

In Table 3-17 below risk characterisation is performed using a PNECaquatic of 6.4 µg/l. This is only a provisional assessment as there is a request to perform a chronic fish test that may change the aquatic PNEC.

Table 3-17: Estimated local PEC/PNECs for the aquatic compartment (including sediment)

Use category	Estimation method	PECaquatic [µg/l]	PEC/PNEC
Production	Site specific, site B	0.11	0.02
Phenolic resins [2]	Site specific, site 4	0.66	0.10
Phenolic resins	TGD	178	**28**
Polycarbonate resins	Site specific, location A	0.10	0.02
Epoxy resins	TGD		
Sub-scenario 1		775	**121**
Sub-scenario 2+3		1.94	0.30
Sub-scenario 4		194	**30**
Regional PEC surface water	TGD	0.095	0.01

2) For site 6 phenolic resin production the PECaquatic could not be calculated and therefore no PEC/PNEC ratio could be established.

<u>Conclusions to the risk assessment for the aquatic compartment:</u>

Conclusion (i) There is a need for further information and/or testing. This conclusion applies to endocrine disruption. Based on in vitro data on ptBP and read across from similar alkyl phenol compounds, including p-tert-pentylphenol, which have shown endocrine disrupting properties in vivo, it is concluded that further testing should be required for ptBP. As a "Tier 2 test" an Extended Early Life-Stage test on fish according to the draft OECD guideline will be performed.

[8] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (i) applies to phenolic resin production site 6 where no site specific data is available and no PECaquatic could be derived. Further exposure information is needed in order to calculate a PECaquatic for this site.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to the life-cycle steps production, for the production of phenolic resins, where site specific data are available, for sub-scenario 2 and 3 of the production of epoxy resins and for the production of polycarbonate resins.

Conclusion (iii) There is a need for limiting the risks, risk reduction measures which are already being applied should be taken into account. This conclusion applies to the generic scenario for phenolic resin production (PEC/PNEC 28) and sub-scenarios 1 and 4 of the epoxy resin production (PEC/PNEC 121 and 30, respectively).

For production of phenolic resins site specific information has been obtained only for about 50 % of the total tonnage used in this use category. Therefore a generic scenario has been conducted which resulted in a risk to the aquatic compartment. The exposure assessment for the production of phenolic resins is based on an average emission factor obtained from the site having the highest emissions participating in the EPRA water monitoring program and on default parameters from the TGD. The size of the site has been chosen in close cooperation with industry. For the sites where site specific information is available no risk has been identified.

Concerning the production of epoxy resins no site specific data have been obtained by industry but only qualitative descriptions of the processes involved. No data on emissions to the environment has been obtained. The information resulted in four sub-scenarios, which have been proposed by industry. TGD default parameters have been used to calculate environmental concentrations. The TGD values have partly been adapted due to information from industry (sub-scenario 4).

Regarding the release from ambient cured epoxy products no further information on releases to the environement has become available.

More site specific information may give evidence of lower emissions than estimated in these two use categories, maybe resulting in no risk. However, no such data has been obtained despite of much effort that has been undertaken by the ptBP producers to obtain this information during the last 1 ½ years.

3.3.1.1 Marine risk assessment

For the marine risk assessment a PNECmarine of 0.64 µg/l is established. According to recent information from industry during the risk reduction phase site 5 , originally reported amongst the phenol/formaldehyde resin production sites, uses ptBP in the production of tri-aryl phosphate esters. The emission scenario had been considered to be comparable to the phenolic resins production scenarios. A marine risk assessment is carried out because these sites emit its treated waste water to a coastal zone (site 5 and 8).

Table 3-18: Estimated local PEC/PNECs for the aquatic compartment (including sediment)

Use category	Estimation method	PECaquatic/marine [µg/l]	PEC/PNEC
Phenolic resins	Site specific, site 5, marine Site specific, site 8 marine	not stated as tonnage confidential < 0.02	**> 1** < 0.03
Regional PEC marine	TGD	0.009	0.01

Conclusion (i) applies to phenolic resin production site 5, where the PEC marine has been calculated using generic parameters and a risk has been identified. The exact value is not given as the tonnage used at this site is considered confidential. Further exposure information is needed in order to refine the PEC marine for this site.

Conclusion (ii) applies to phenolic resin production site 8. The local PEC marine for this site is below 0.02 µg/l. The PEC/PNEC ratio is below 0.03.

Conclusions ii) for the aquatic compartment has to be seen as provisional until possible endocrine effects in fish have been resolved.

3.3.1.2 PBT assessment

In the PBT assessment the following criteria are used to decide if a substance must be regarded as a PBT substance.

- P (Persistence): Half-life > 60 d in marine water or > 40 d in freshwater or half-life > 180 d in marine sediment or > 120 d in freshwater sediment.
- B (Bioaccumulation): BCF > 2,000.
- T (Toxicity): Chronic NOEC < 0.01 mg/l or CMR or endocrine disrupting effects.

Substances are selected when they fulfil the criteria for all three inherent properties. PtBP is regarded as readily biodegradable (not fulfilling the 10 day window), the BCF is less than 2000. The T criterion is fulfilled since ptBP is agreed classified as toxic for reproduction (category 3). However, for a selection as a PBT substance all three criteria have to be met.

3.3.1.3 Microorganisms in STP

A PNEC of 1.5 mg/l is established for effects on microorganisms in STP. In Table 3-20 the PEC/PNEC for the different use categories are shown.

Table 3-19: Estimated local PECs for the STP compartment. Only highest value estimated is presented for each use category.

Use category	PECSTP [mg/l]	PEC/PNEC
Production (site B)	0.02	0.01
Phenolic resins (water monitoring program)	≈ 0.01	0.007
Phenolic resins (site 8, LOD)	0.01	0.007
(Site 5)[1]	not stated as tonnage confidential	**> 1**
Phenolic resins (site 6)[2]	-	**-**
Phenolic resins (TGD, generic scenario)	1.78	**1.2**
Polycarbonate resins, location A	0.0013	$8.7*10^{-4}$
Epoxy resins (TGD generic scenarios)		
Sub-scenario 1	7.75	**5.2**
Sub-scenario 2+3	0.02	0.01
Sub-scenario 4	1.94	**1.3**

1) For site 5 ptBP is used in the production of tri-aryl phosphate esters. The emission scenario is considered to be comparable to the phenolic resins production scenarios.
2) For site 6 phenolic resin production the PEC_{STP} could not be calculated and therefore no PEC/PNEC ratio could be established.

Conclusion (i) applies to phenolic resin production site 5, where the PEC_{STP} has been calculated using generic parameters and a risk has been identified. The exact value is not given as the tonnage used at this site is considered confidential. Further exposure information is needed in order to refine the PEC_{STP} for this site.

Conclusion (i) also applies to phenolic resin production site 6, where no site specific data is available and no PEC_{STP} could be derived. Further exposure information is needed in order to calculate the PEC_{STP} for this site.

Conclusion (ii) applies to sewage treatment plants for the production of ptBP, for the production of phenolic resins where site specific data are available, for sub-scenario 2 and 3 for the production of epoxy resins and for the production of polycarbonate resins.

Conclusion (iii) applies to the generic scenarios for phenolic resin production (PEC/PNEC 1.2) and sub-scenarios 1 and 4 of the epoxy resin production (PEC/PNEC 5.2 and 1.3, respectively).

3.3.2 Terrestrial compartment

The PNECsoil is 73 µg/kg wwt based on the equilibrium partitioning method. As indicated in Table 3-20 the two use categories phenolic and epoxy resins result in exposure to agricultural soil via sludge application.

Table 3-20: Estimated PEC for agricultural soil for scenarios estimated according to TGD default assessment

Use category	PECsoil [µg/kg] wwt	PEC/PNEC
Phenolic resins - generic	1,110	15
Epoxy resins - generic		
Sub-scenario 1	4,830	66
Sub-scenario 2+3	20	0.27
Sub-scenario 4	1,210	17

No risk characterisation for industrial soil has been carried out.

Conclusion (ii) This conclusion applies to the generic scenario for epoxy resin production sub-scenarios 2 and 3.

Conclusion ii) for the terrestrial compartment has to be seen as provisional until possible endocrine effects in fish have been resolved.

Conclusion (iii) This conclusion applies to the generic scenarios for phenolic resin production (PEC/PNEC 15) and sub-scenarios 1 and 4 of the epoxy resin production (PEC/PNEC 66 and 17, respectively).

3.3.3 Atmosphere

No risk assessment for the atmospheric compartment has been conducted.

Conclusion (ii) applies to atmospheric compartment. Although some release to air is reported for one production site and release to air is assumed using default release fractions in the TGD, the properties of ptBP indicate that this compound will rapidly degrade or be transferred to the aquatic compartment. No additional information is assumed necessary with respect to the air compartment.

3.3.4 Secondary poisoning

No risk assessment for secondary poisoning has been performed.

Conclusion (**ii)** available data indicate that ptBP is unlikely to bioaccumulate in the food chain. No further information is considered necessary.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Overview of exposure

PtBP is used as a chemical intermediate, for example, in the manufacture of ptBP/formaldehyde resins or polycarbonate. The industry sectors where occupational exposure to ptBP may occur are:

Scenario I: Production of ptBP;
Scenario II: Users of ptBP as an intermediate (formulation and processing)
- phenolic resins producer
- polycarbonate producer
- epoxy resins producer
- producer of chemicals used in synthesis.

Scenario III: Professional end uses as for example use of resins and paints.

PtBP is manufactured and processed in closed systems/processes. The situations giving rise to occupational exposure are likely to be similar for both manufacturers and processors (formulators) (i.e. closed systems with some breaching).

According to information from the Norwegian Product Register ptBP is registered in 207 products with a total amount of ptBP of 3.8 tons in 2003, see also table 2.2.

Consumer uses have been identified for adhesives and paint and varnishes, table 2.3. For further discussion see chapter 4.1.1.3.1.

4.1.1.2 Occupational exposure

The main routes of exposure for workers are expected to be by inhalation and dermal contact. Ingestion is not considered to be relevant for occupational exposure.
PtBP will be handled and used both in molten and solid form and workers might be exposed to vapour, liquid or dust.
Data based on measurements are preferred when assessing exposure in the working atmosphere. However, for several of the scenarios insufficient measurement data were available from the industry and literature. Due to the low number of measurements, all available data have been presented.
For scenarios where there are few available measurements or no measurements at all, modelled data are used. The exposure levels have been calculated by the EASE (Estimation and Assessment of Substance Exposure) program, by applying default values from Marquart et al. (2006) and by the TGD Appendix IE dermal exposure. No measured data is available for dermal exposure. However, the study by Kosaka et al [(1)] (1989) suggests that dermal absorption of ptBP can be substantial. See also point 4.1.2.1.2.

All values for ptBP-concentrations are given in mg/m^3. Data originally reported in units of ppm, have been converted to the units of mg/m^3, by use of the conversion factor 1ppm=6.24mg/m^3 ([mg/m^3] = 1 [ppm] x 150,2 [g/mol]/24,05526 [l/mol] = 6.24 [mg/m^3]

Table 4.1 Occupational exposure limits.

Country/ organisation	8 hour TWA	Short term value	Reference
European Union	_	_	Commission Directive 91/322/EØF Commission Directive 2000/39/EC
ACGIH	_	_	Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. 2002.
Germany (MAK)	0,5 mg/m^3 (0,08ppm)	_	Deutsche Forschungsgemeinschaft, 2002. List of MAK and BAT Values 2002. Classification dates from 1981, 1995.
Sweden	_	_	Arbetarskyddsstyrelsens Författningssamling, 2000
Netherlands	0.5mg/m^3	_	Netherlands. National MAC List, 2003
Austria	0,5 mg/m^3 (0,08ppm)	0,4ppm (2,5 mg/m^3) 30 minutes, 2 times per shift	Bundesgesetzblatt für die republik Österreich. Grenzwerterordnung 2001-GKV 2001.
Denmark	0,5 mg/m^3 (0,08ppm)		Denmark. National Labour Inspectorate. Exposure Limit Values For Substances and Materials. Instruction No. 3.1.0.2. Dec 1996. [Arbejdstilsynet. Grænseværdier for Stoffer og Materialer. At-Anvisning. Nr. 3.1.0.2. Dec 1996.]
United Kingdom	_	_	Health and Safety Executive, UK, 2000 (EH40/2000)
Norway	_	_	Norwegian Labour Inspection Authority. Guidance on administrative norms for pollution of the working atmosphere. October 2003 [Veiledning om administrative normer for forurensning i arbeidsatmosfære. Mai 2000]
Switzerland	0,5 mg/m^3 (0,08ppm)	0,4ppm	Source: RTECS, 2002 (January 1999)

Abbreviations: TWA = time weighted average.

In addition there is a Biological Limit Value, the German BAT value of 2 mg ptBP/l urine.

4.1.1.2.1 Occupational exposure from production

Scenario I

There are 3 producers of ptBP in Europe. Production sites are located in Germany, France, and Switzerland. Although Switzerland is not a member of the EU, the production site in Switzerland is included for the risk assessment. One producer uses also ptBP captive on site.

From 2004 there are only two producers. In consultation with industry it has been agreed to maintain the 2001 figures in the RAR for confidentiality reasons. Moreover, no updated figures for the 2004 situation are available and therefore the data from 2001 are used.

The production process used by all producers is the same. Phenol and isobutene are reacted in the presence of a fixed bed ion exchange resin in either a continuous process (2 producers) or a batch process (one producer). Following reaction the product is distillated to eliminate unreacted starting materials (these are recycled to the reactor). In a second distillation step the final product is separated. The pure product can be stored as a molten product at 130°C and shipped in trucks. The molten product can also be processed to flakes in a strictly closed system. The flakes are automatically filled into 20kg bags or big bags. More details are given in chapter 2.1.1.
The manufacture of ptBP is carried out in closed systems. It is estimated that about 15 workers are involved in the production process with more than 50 % of their working hours, and additional 20 workers with less than 50% of their working hours (the estimation is based on questionnaires: information available from all producers).
Occupational exposure arises during tasks where the system is breached, for example, sampling, maintenance and product filling to drums or tankers. PPE used for the different working operations is specified in appendix A.

Inhalation exposure

Measured data

Exposure data for ptBP were received from the two producing companies and one former producing company.

Producer A, reported peak values of 0.5 – 1.5 mg/m^3 during "filling/emptying/transferring" operations. The personal protection used was reported to be gloves, goggles, respirators, and protective suits. During all other operations, e.g. weighing/mixing, storage, sampling, maintenance and laboratory operations much lower concentrations were reported. The measured values are reported to be in the range of 0.01 – 0.3 mg/m^3. Measurements have been performed over the past 10 years. Personal protection measures include gloves and goggles, as well as protective suits during weighing/mixing, transport of closed containers, and during sampling.

Producer B provided monitoring data for maintenance operations. In 1998 four measurements were performed. The median concentration was found to be below 0.04 mg/m^3.
Personal and engineering protection measures are reported to include gloves, goggles, respirator, and protective suit during maintenance and laboratory operations (except respirator).

Producer C provided recent data (year 2002) from the production area. Personal measurements were performed (over an 8 hr shift). The detection limit of the method was

reported to be 0.05 mg/m^3. Concentrations of 0.15 and 0.14 mg/m^3 were reported. Information on personal and engineering protection measures is also available. It includes gloves, goggles and protective suits for all operations, as well as respirators during maintenance.

One producer provided following values, but has not presented information about the measurements (no information about numbers of samples, sampling period etc). The measured values were not presented with sufficient information on measuring parameters and cannot be taken into account, but just give some indication. The level for tank filling probably represents short periods and is similar to the upper EASE estimate for this task. The level given for packaging is based on stationary measurements on an automatic bag-filling machine in an enclosed area. No information on operator entering this area e.g. for maintenance have been given:

a) Sampling from a plant equipped with low-emission sampling valves gave measured values <1.9 mg/m^3. (20 process samples a day, sampling period 30 seconds)

b) Filling in tank containers/tank cars; loading of ptBP melt is reported to give values around 18.7 mg/m^3. Measurements were taken when undocking the loading unit and the dome cover was opened briefly for less than 1minute and vapours with a pressure of ca 10mbar was released.

c) Packing (flaking by a cooling roller and filling) indicated levels of 3.1 mg/m^3. The flakes are stored temporarily in a silo at ambient temperature. The silo is protected from the atmosphere by a 30mbar overpressure control valve, so that no emission will occur during normal operation. From the silo, the flakes are fed through an airtight sluice over an automatic balance into an automatic bag-filling machine for 20 kg PE bags. The 20 kg PE bags are automatically palletised. The automatic bag filling equipment is enclosed in a cabin in which the air is changed 6 times per hour. The off-gas is purified over an effective filter system and is released into the atmosphere from the roof. The off-gas system is obligatorily coupled to the bagging machine, so that bagging cannot occur in the absence of off-gas cleaning. Concentration measurements at the exit of the filter system indicated a ptBP level of ca. 3.1 mg/m^3. The filling system is operated discontinuously when required (ca. 150 days per year).

d) Maintenance: Leakage at pumps used to pump the ptBP melt occurs only rarely (not more than once a year). Leakage is avoided by using enclosed pumps (double mechanical axial face seals with leak detection or magnetic pumps). Moreover, any leaked p-tert-butylphenol solidifies immediately at the ambient temperature and then has a vapour pressure of < 5 mbar. Before a defective pump is removed for repairs, the pump housing is evacuated to remove all residues and is flushed with nitrogen to free it from all traces of the product. The heating is then turned off so that any residual product solidifies and the pump can be detached without any significant emission. Measurements on employees yielded values of < 3.1mg/m^3 ptBP.

e) Laboratory: Work in the laboratory is performed in fume hoods. PtBP concentrations of < 0.6 mg/m^3 have been measured in the air of the laboratory. The laboratory is used for 7 hours during the day from Monday to Friday.

Safety measures: PPE is used regularly. See appendix A. Showers after work are compulsory for all employees. Changing rooms are divided into a black shed (for work clothing) and a white shed (for street clothing). Creams for skin protection and skin-cleansing agents are

provided in accordance with a skin protection programme. Workers exposed to ptBP are given a medical examination (blood, urine, liver and skin status) once a year to check for occupational damage or injury. No case of skin depigmentation has occurred in the factory since the reaction parameters, including the catalyst system, were optimised in 1987 and 1988 and the purity of the product improved to > 99.5 %.

Table 4.2 Production of ptBP - measured values

Activities/events	Measured values air samples Median mg/m^3 Range mg/m^3 (no of measurements)	95-Percentil mg/m^3 sampling period P=personal A=area	Comments
Production operators	0.14 0.14-0.15 (2)	8 hours sampling, P	Measurements were done in 2002
Maintenance	<0.04 (4)	4 hours sampling	Measurements were done in 1998
Maintenance	 <0.01-0.08 (>10)	TWA, P	Measurements were done over the past 10 years, starting 1994.
Filling/emptying/ transferring	0.5-1.5 (> 10)	STV, P	
Weighing,mixing	 <0.1-0.3 >(10)	0.2, TWA, P	
Storage	<0.02-0.05 >(5)	TWA, A	
Process,sampling	 <0.02-0.2 >(10)	STV, P	
Laboratory operations	 <0.01-0.05 >(3)	TWA, A	

STV= short term value, TWA = time weighted average

SIDS (May 1996, Sponsor Country: Japan) reported the values given below from two production facilities. The workers wore respiratory protecting equipment and protective gloves during sampling, bag filling, and coupling and decoupling operations from tank loading. The bag filling operation was done semi-automatically except bag handling in the building which had a local exhaust ventilation system. Other operations were done in open space. Air samples were collected from the workers breathing area using silica gel tubes and analysed in the laboratory by High Pressure Liquid Chromatography with UV detection.

Table 4.3: Inhalation exposure from two production facilities (SIDS)

Working Procedure	Number of samples	Frequency and duration of working operation	Average conc mg/m^3	Range mg/m^3
Sampling	9	6x 1 min/day	7.3	<0.1-32.3
Bag filling	10	20x8.5 hours/month	0.1	<0.1-0.2
Bag filling	unknown	7 hours/day	0.22	
Tank loading	2	7x40 min/month	0.3	0.2-0.3

Biological monitoring: See also point 4.1.2.1.2 on studies in humans.
PtBP is excreted rapidly in urine (biological half life ca 4 hours (Ikeda et al, 1978)) and can be analysed in urine by GC with a detection limit of 0.2 µg/ml (ref in IUCLID Datensatz 2000).

A Japanese study (Ikeda et al, 1978) has reported urine levels in workers in a plant producing ptBP (Table 4.4). The levels were reduced by the improvements of hygienic working conditions in the workshops. Airborne levels in the working areas were not reported. A biological threshold limit is suggested of 2 µg/ml based on an air concentration of 5 mg/m^3. Urinary levels (GM) 1.2 µg/ml for plant operators, 6.3 µg/ml for packers and 0.5 µg/ml for engineers were reported. Preventive measures (semi-automation of weighing, and bag sealing, and local exhaust system) decreased urinary levels in engineers (trace) and packers (by 65%).

Table 4.4: PtBP levels in urine of production workers in relation to hygienic working conditions (µg/ml urine).

Workplace conditions	Urine Samples	Plant operators (n=11) median (range)	Engineers (n=7) median (range)	Product packers (n=9 or 7) median (range)
Original	During the shift (exposure)	1.2 (0.5-3.0)	0.5 (0.2-1.2)	6.3 (1.8-21.7)
	During the exposure- free time	0.6 (nd-6.0)	Tr (nd-0.4)	3.5 (1.0-12.1)
Improved	During the shift (exposure)	1.3 (0.4-3.6)	Tr (nd-1.0)	2.2 (0.7-6.7)
	During the exposure- free time	0.8 (nd-2.3)	Tr (nd-0.6)	1.8 (0.6-5.6)

n= number of workers, nd= not detected, Tr= trace

Kosaka et al (1989) investigated airborne and urinary levels in operators in a ptBP producing plant using respirators.
Airborne levels (GM) of 0.39 mg/m^3 for packers were reported and 0.10 mg/m^3 for carriers. Urinary levels (GM) of 5.1 µg/ml for packers and 3.0 µg/ml for carriers were reported. The correlation between urinary and airborne levels was moderate (r=0.46) Assuming an efficiency of the respirators of 50-60%, the renal excretion was approximately 2-3 times higher than expected from inhalation, which could indicate significant dermal absorption; ptBP levels in air and urine are shown in table 4.5
Sampling was done on 10 workers in the product packaging department and four persons involved with transport. All workers wore respirators.

Table 4.5: PtBP level in air and urine among workers packing ptBP

Collective	Shift	ptBP conc. (mg/m^3) in the workplace air (8-hour value) Geometric mean (range)	ptBP excretion in urine mg/l*
Workers in the product packaging department	Dayshift (n = 9)	0.39 (0.28 – 0.53)	4.20 (2.01 – 8.78)
	Nightshift (n = 6)	0.39 (0.20 – 0.76)	6.12 (4.01 – 9.36)
Employees who carry out transport work	Dayshift (n = 3)	0.12 (0.09 – 0.16)	2.58 (1.87 – 3.57)
	Nightshift (n = 2)	0.08**	3.56 (0.65 – 19.4)

n=number of workers

* Urine samples, collected in the 2nd half of the shift, values corrected to a spec. weight of 1.024

** Only two measurements are available

Conclusions:

- Two published studies of ptBP production workers indicate similar urinary ptBP levels
- Calculations on excreted ptBP and the uptake from airborne exposure suggest that a major route of exposure is through the skin

Biological monitoring data on ptBP levels in urine of workers with potential contact with ptBP has been provided by one European producer. The monitoring was conducted during 1987- 2002 and show a decrease in mean value from 1.17 mg/l to 0.068 mg/l. The decreasing trend in urinary levels indicates that technical measures and the use of PPE have lowered worker exposure.

Modelled data

Modelling with EASE

Since the system is a full containment, there is a low level of exposure during operation. The system is fully automated, and no systematic maintenance is executed on a regular basis. The data below are estimated from the information given by the industry.

In addition to the closed production, there is one scenario: "Sampling"

Sampling is executed during full production, where the process temperature is 120 ^{0}C. The ptBP is then a liquid. The operations are performed by skilled personnel. There is local exhaust ventilation available. The predicted vapour exposure is then 3.1-18.7mg/m^3.

One producer informs that there will be no exposure to ptBP during transfer of ptBP from reactor to buffer (storage) tank. The transfer is done in a strictly controlled closed system. Industry confirms that this applies for all three production sites, and the short term values referred above are therefore not relevant.

Table 4.6 EASE calculations

Activity	Process temp	Significant breaching	LEV	EASE conc estimate mg/m^3
Production	120^{o}C liquid	False	Closed system	0-0.62
Sampling	120^{o}C liquid	True	Personnel LEV	3.1-18.7

Dermal exposure

6 cases of vitiligo were reported in 1984-1987 at a production site where ptBP production was manufactured by a semi-continuous and not entirely closed process. The molten ptBP was pastilled and filled into bags by not completely closed devices. No cases of vitiligo were observed after changing the process to a closed-process and the purity of the material increased. When ptBP is handled in molten form (at 120°C) dermal exposure will not be assessed, in accordance with the TGD.

Measured data

No measured data available

Modelled data

Summary/statement of the exposure level for scenario I – production

The highest measured value from the product packing department of 0.76 mg/m^3 is taken forward to the RC for scenario 1 as a reasonable worst case and 0.39 mg/m^3 as a typical value. The data set of 15 measurements represents the average exposure of both day and night shift workers and may give a better estimate of exposure than modelled values by EASE.

19 mg/m^3 is taken forward as a reasonable worst case for short term exposure as estimated by EASE for sampling and filling. The measured value of 7.3 mg/m^3 is taken foreward as typical short term value for sampling.

4.1.1.2.2 Occupational exposure from formulation and processing

Scenario II

The following scenarios are discussed:

II.1 Production of polycarbonates

II.2 Production of phenolic resin

II.3 Production of epoxy resin

II.4 Production of chemicals used in synthesis

Many of the production procedures include use of other hazardous chemicals such as formaldehyde and phosgene that make strict controlled processes necessary.

Scenario II.1. Production of polycarbonates

Two companies in Europe use ptBP in their polycarbonate production (3 production sites). PtBP is used as a chain terminator in the synthesis of polycarbonate polymers to adjust the molecular weight of the polymer. Polycarbonate resins produced with ptBP contain 1-3 wt % of ptBP reacted and bound into the polymer chain.

The process involves stirring bisphenol-A and the chain terminating agent in a mixture of methylene chloride and water, while adding phosgene in the presence of a catalyst. Sodium hydroxide solution is added to maintain the correct reaction pH. The by-product of the reaction is sodium chloride, which concentrates in the aqueous phase. See point 2.2.2.1 for more information about the process. The polymer is isolated as dry granules, prills or flakes.

The polycarbonate production at all 3 sites is a fully automated process in strictly controlled closed-systems.
P-tert-butylphenol is transferred from ISO or road tanks at an open air unloading station. An unloading arm is used to transfer the molten p-tert-butylphenol in a storage tank. Since p-tert-butylphenol is used as a chain terminating agent in the production of polycarbonate, it is fed directly in the reaction and consumed.

About 20 workers are involved in the processes with more than 50 % of their working hours. Up to 200 workers are involved with less than 50% of their working hours.

Unloading of p-tert-butylphenol is done by 1-2 persons per shift with less than 50% of their working hours.

Protective gloves and goggles are worn for all operations. In addition, respirators and protective suits are used for those operation steps where required (e. g. unloading, maintenance etc.). PPE is worn during the different working operations. See appendix A for specification.

The residual concentrations of non reacted p-tert-butylphenol in polycarbonate have been measured. The concentration was found to be non detectable, at a limit of detection of 5ppm.

Inhalation exposure

Measured data

Monitoring data are available for all three sites.
For Company A during the unloading step (operation step with higher likelihood of potential exposure) concentrations were found to be in the range of < 0.03 – 0.11 mg/m^3 (59 measurements). The 95 percentile is 0.11 mg/m^3 and the median is <0.03 mg/m^3.
The unloading station is located in open air. Unloading takes place 2-3 times a week. When unloading, the ISO tank is connected to the unloading arm and vent connection arm. Leak test is performed with nitrogen. The ISO tank is pressurized up to 1 bar with nitrogen as a pad and is padded during unloading (blanket). Liquid ptBP is pumped from the ISO tank directly into a heat traced storage tank. Total unloading time is approximately 1.5 hours. All equipment in

closed nitrogen padded system is connected to the plant vent system where the vapours are incinerated. The workers use PPE (splash suit, gloves and breathing protection- during the connection and disconnection operation (ca 15 min each). In between the workers are standby in the control room watching the process via a camera.

For company B there are two production sites. Since the process is chemical and technical identical at both production sites the data can be considered to be representative for both sites. At production site A measurements are available from the production area also including unloading of ISO-tank containers. Monitoring data from people working in the production were found to be in the range of < 0.005 – 0.014 mg/m^3 (n = 18). The 95-percentile is 0.013 mg/m^3 and the median is <0.005 mg/m^3. This group included shift supervisor, supporting supervisor, outside operator, day operator production and laboratory technician taking samples. In other workers (mechanical and electrical technicians) the concentrations were in the range of < 0.005 – 0.007 mg/m^3 (n = 6; median <0.005 mg/m^3). At production site B, measurements of the unloading process were conducted. Personal monitoring data (3 measurements) reflecting the unloading process (1-1.5 hours) were found twice to be non detectable with detection limits of 0.09, 0.1 and once to be 0.18 mg/m^3.

Table 4.8 Measured data at production site of polycarbonate resins

Activities/events	Measured values air samples Median mg/m^3 Range mg/m^3 (no of measurements)	95-Percentil mg/m^3 Sampling period P= personal A=area	Comments
Unloading of ISO-tank containers, open air	<0.03 <0.03-0.11 (59)	0.11,STV, A 1.5 hours (unloading 2-3times/week, temp=120°C)	Measurements were done over the period 1993-1997
Production operators (includes also unloading of ISO-tank containers)	<0.005 <0.005-0.014 (18)	0.013 TWA, P	Measurements were done in the period of 1999-2000
Mechanical and electrical technicians maintenance, laboratory operations)	<0.005 <0.005-0.007 (6)	TWA, P	Measurements were done in the period of 1999-2000
Unloading of ISO-tank containers, open air	<0.09-0.18 (3)	STV, P 1-1.5 hours (unloading 2-3/ week, temp=120°C)	Measurements were done in August 2002

STV= short term value, TWA=time weighted average

Modelled data

EASE estimates an exposure in the range of 0 – 0.624 mg/m^3 for a closed system. The operation is carried out 2-3 times a week and the task last for about 2 hours.

Table 4.9 EASE calculations

Activity	Temp	Significant breaching	Pattern of control	EASE conc estimate mg/m^3
Unloading PTBP from ISO tanks	120^{o}C liquid no aerosol formation	False	Full containment Closed system	0-0.624

Dermal exposure

Measured data
No measured data is available.

Modelled data

Because of the high temperature of the molten ptBP, dermal exposure is only likely to occur from accidents and therefore negligible. See TGD 2.2.5 figure 2, dermal exposure assessment scheme.

Summary/statement of the exposure level for scII.1-formulation of polycarbonate *resin*

The 95 percentile of 0.013 mg/m^3 is taken forward to the RC as a reasonable worst case for a full shift. The dermal exposure is considered negligible because of the closed process and liquid with temperature of 120^{o}C is treated. Unloading of ptBP from ISO-tanks, give rise to some exposure. The operation last fcor 1-1.5 hours 2-3 times a week An EASE estimate for unloading gives a value 0.6 mg/m^3. This value is taken as a RWC for short-term exposure. The 95 percentile from measurements gives a value of 0.11 mg/m^3. This value is taken as the typical concentration.

Scenario II.2. Production of phenolic resin

Butylphenol is used in phenol/formaldehyde resins, either alone or mixed with other phenols. Phenol/ formaldehyde resins manufacture is based almost exclusively on discontinous batch processes and the batch processes and the batch process uses a traditionmal reactor or 'kettle'.

Depending on the formulation, the process and the heat stability of the resin, reactor size can vary from 1 to 40 m^3.
PtBP is normally introduced into the reactor as a molten liquid from storage tanks via a closed system. In small scale production sites solids may be loaded from bags, in which case dust extraction will be necessary to protect workers from exposure. Normally evaporation equipment is installed to avoid exposure.

There are essentially two main approaches in common use. The 'en-masse' approach involves the addition of the total requirement of main reactants necessary to complete the reaction at the outset. The reaction is initiated by the addition of the catalyst and the subsequent application of heat. The continuous addition or semi-batch process involves the controlled addition of one of the raw materials during the reaction phase. Most typically, the reactant introduced gradually is formaldehyde, since it is usually in solution form.

In some cases a combination of both processes may be employed. The reaction may also be conducted in solution in (e.g.) xylene.

The final resin will be discharged:

- as a solution in an organic solvent, for example, xylene - the solution will be transferred into drums, IBCs or tanks or
- as a molten solid into a cooled tray -the solidified resin will be broken up and packaged or
- as flakes or pastilles on to a cooled belt - these will be packed into (e.g.) bags or FIBCs or
- as an aqueous dispersion, packed into drums, IBCs or tanks.

The use of formaldehyde makes it obligatory to use controlled closed systems. Therefore it can reasonably be assumed that the releases and resulting concentrations in the air are low**.** The residual concentration of non-reacted ptBP in phenolic (phenol/formaldehyde) resin may be up to 3% free ptBP (Data given for oilfield chemicals).

Personal and engineering protection measures are reported. The personal protection equipment includes gloves and goggles for almost all operations, with additional equipment like protective suits and respirators if necessary.

One producer reported that the whole production process is performed under full containment. At least gloves and goggles are used during all operation steps. If necessary, additional PPE's (respirator, protective suits) are used as well. Approximately 20 persons (males only) are involved in the production process, with less than 50 % of their working hours. (Reference is not given).

Inhalation exposure

Measured data

Ebner et al. (1979) reported ptBP concentrations of 0.12 – 0.96 mg/m^3 (n=5) measured stationary in the working zone of operators of a phenolic resin plant charging reactors with ptBP in bags. Natural ventilation and local exhaust ventilation through the charging opening. No reliable monitoring data for the current used processes are available.
One producer of resins reported that area concentrations during transferring of ptBP have been measured to be below 0.05mg/m^3 (3 hours analysis at a fixed point, no personal measurement).
Industry informs that one producer has a semi-automated, manual process, temperature max 110 ^oC and batch production. 6 persons work continuously. No information about exhaust ventilation is available.
On operator measurements for 6 hours at one site gave values of 0.22 mg/m^3 (total resin dust) for bagging operations.

Table 4.10 Measured data - production of phenolic resin

Activities/events	Measured values air samples	95-Percentile mg/m^3 sampling period	Comments

	Median mg/m^3 (range mg/m^3) (no of measurements	P= personal S=stationary	
Production	<0.05 (1)	TWA, A Sampling period:3 hours	Measurements were done in 2002
Charging reactors with ptBP in bags	0.12-0.96 (5)	Sampling period not known. S	

TWA= time weighted average

Modelled data

Ease estimates an exposure in the range of 0 – 0.6mg/m^3 for a closed system (table 4.12). Two operations are described in data from the industry: Maintenance and filling of the reactor.

Maintenance is executed in ambient air on a frequency of every 6 months with a duration time of 2 hours. The ptBP is introduced as molten, therefore no dust exposure can occur. Ventilation is present.

When filling the reactor, one producer informs that the temperature is 120^{o}C. The frequency is three times a day for, duration of one hour. Ventilation is present, and it is performed outdoor. But ptBP may also be loaded as a solid from bags either manually or semi-automated at room temperature. EASE calculations have been done for loading of both liquid and solid.

Table 4.11 EASE calculations

Activity	Temp.	Dust type	Contact level	Use Pattern	Pattern of control	EASE conc estimate mg/m^3
Filling the reactor	25^{o}C Mobile solid	Inhalable size Non-fibrous Non-aggregating	Intermittent	Dry mani-pulation	LEV present	2-5

Table 4.12 EASE calculations

Activity	Temp.	Use Pattern	Pattern of control	EASE conc estimate mg/m^3
Production closed system	120 ^{o}C liquid no aerosol formation	Closed system No breaching	Full containment	0-0.6

Dermal exposure

No measured data is available.

Modelled data

Table 4.13 EASE calculations

Activity	Temperature	Contact level	Use pattern	Pattern of control	EASE conc estimate mg/cm^2/day
Filling the reactor	25^{o}C mobile solid	Intermittent	Non dispersive	Direct handling	0.1-1

Dermal exposure to a hot liquid will not be done without wearing protective gloves. The exposure is considered negligible. Exposure to solid at room temperature could give rise to exposure at the highest EASE values. Palms and fingers will be exposed and assumed exposed surface area is 420 cm^2.

Summary/statement of the exposure level- ScII.2 formulation of phenolic resins

Since almost no measurements have been presented, the EASE values are taken forward to the risk characterisation. For a fully automated production, the highest EASE value of 0.6 mg/m^3 is brought forward for a reasonable worst case inhalation exposure.
When loading hot liquid the dermal exposure is considered negligible.

Scenario II.3.Production of epoxy resin

Four different uses of ptBP in the epoxy industry have been identified:

1. Starting material in the manufacturing of ptBP glycidylether (ptBP-GE) used as reactive diluent / thinner in epoxy resin systems
For the production of ptBP glycidylether the ptBP is reacted with an excess of epichlorohydrine (under alkaline conditions). The glycidyl ether normally contains about 5 – 10 % of unreacted ptBP.The ptBP-GE is used in concentrations of about 10 – 30 % in the final epoxy resin system to reduce the viscosity. No occupational exposure measurements are available.

2. Accelerator in hardening agents for epoxy resins based on amines
For the production of the hardening agent ptBP is added to the amine component (about 5 – 20%) and solved by warming.
The amine salt is added to the epoxy resins in concentrations of 30 – 50 %. Following the hardening process the concentration of ptBP is in the range of 4.6 – 6.7 %.
If used as an accelerator in the hardening process without heating residual ptBP is not chemically/covalently bound in the matrix but closely bound in the matrix. The matrix itself is completely insoluble in water and migration of the free ptBP does not occur.

3. Starting material in the production of "Mannich bases" used as hardening agents for epoxy resins
"Mannich bases" are used as hardening agents (for a fast hardening process) in the epoxy resins industry. For the production of the "Mannich bases" ptBP is reacted with the amine

component and formaldehyde. The final reagent may contain unreacted ptBP (up to 30 %) as well as amine.
Using a blend of about 100:40 or 100:50 (epoxy resin:"Mannich reagent") the concentration of residual ptBP in the final epoxy resin is in the range of 8.6 – 10 %.
Residual ptBP is not chemically/covalently bound in the matrix but closely bound in the matrix. The matrix itself is completely insoluble in water and it has been shown for high temperature cured epoxy formulations that migration of the free ptBP does not occur. There is uncertainty about ambient cured epoxy formulations.

4. Modifier/chain terminator in the manufacturing of epoxy resins
PtBP is used to a limited extent as chain modifier in the manufacturing of certain epoxy resins. PtBP modified epoxy resins are used as polymeric binder in industrial corrosion protective coatings (ambient cured epoxy coatings, epoxy powder coatings, heat cured coatings). In this application, the ptBP is fully reacted to the epoxy backbone and residual levels of unreacted ptBP in the epoxy resin are extremely low (typically in the ppm range). A release of ptBP from crosslinked epoxy systems into the environment is unlikely to occur.

No detailed information is available on occupational exposure. However, it can reasonably be assumed that the exposure situation is similar compared to the phenolic resin production.
One (smaller) epoxy resin producer informs that manufacturing takes place in a closed reactor. Although the process is fully automated, charging of the reaction vessels occurs manually. Workers are potentially exposed to ptBP during manual charging of ptBP from 20 kg bags into the open manhole of the epoxy reactor (takes up to 1 hour/shift). All other raw materials are charged automatically in closed systems. During the manual charging of ptBP workers wear adequate personal protective equipment (gloves, full face respirator or protective suit). The production of epoxy resins is done in batches (once/month). One worker is involved in this process.

Inhalation exposure

Measured data

Very few personal measurements have been presented from industry.
Monitoring data without sufficient information on measuring parameters are available for the operation step where ptBP is filled to the reactor vessels. Air is collected on silicagel tubes at flowrates up to 1 l/min. Sampling was conducted over periods of 10 – 45 min. Concentrations of 0.002 – 0.08 ppm (0.012-0.48 mg/m^3) have been determined.
Monitoring was done for filling operations (ptBP charging from 20 kg bags to epoxy reactor). A worst case short term exposure monitoring was conducted. Measurements took place from August – December 1991. Air was sampled by collection at flowrates up to 1 l/min on silicagel tubes, desorption with diethylether containing 10% methanol and subsequent GC chromatography; the detection limit was 0.5 – 1 µg/tube. The sampling method described is not relevant if dust is liberated.
Personal measurements have been presented from two epoxy resin producers.
From Producer A the samples were taken when 600 kg solid ptBP were loaded to a reaction kettle. The worker carried sampling devices for both dust and organic vapour from the beginning of the loading operation to the end. Local exhaust ventilation worked properly during the operation and the worker used personal protective equipment (gloves and dust/organic vapour mask). The working operation was considered to give the highest

occupational exposure during the production. The operation took place 4-5 times during the entire year 2004 and normally lasted for 30-38 minutes each time. For the production of other types of epoxy resins, lower amounts of ptBP (50-325kg) will be transferred to the kettle and give shorter exposure periods. Only one measurement was performed with a dust concentration of 1.228 mg/m^3 and 0.261 mg/m^3 in the vapour phase, giving a total concentration of 1.491mg/m^3.
Producer B used both a wet and a dry production process. Occupational exposure measurements have been conducted in an area with highest potential exposure, and both personal and area samples have been collected. No details have been provided concerning the measurements, and it is not clear which phases have been measured. Concentrations from 0.26-0.9mg/m^3 (stationary samples) and 0.29-6.6mg/m^3 (personal samples) were reported.

Modelled data

EASE values for workers handling 20 kg bags during manual charging, are as follows:
The process temperature is 25 0C and the physical state of ptBP is solid. Dust emissions will then be a problem. Particles, which are liberated into the air, are in the inhalable size range. The operations are dry manipulation. Ventilation is present. The exposure will then be in the range of 2-5 mg/m3.

Table 4.14 EASE calculations

Activity	Temp.	Dust type	Contact level	Use Pattern	Pattern of control	EASE conc estimate mg/m^3
Manual charging	25^{o}C Mobile solid	Inhalable size Non-fibrous Non-aggregating	Intermittent	Dry mani-pulation	LEV present	2-5

Dermal exposure

Measured data

No measured data are available

Modelled data

EASE values for workers handling 20 kg bags during manual charging, are as follows:

The process temperature is 25 0C and the physical state of ptBP is solid. The exposure type is dermal and the pattern of control is direct handling. If the contact level is intermittent the dermal exposure is predicted to be in the range of 0.1 – 1 mg/cm2. Exposed surface area is assumed to be 420 cm2 (palms and fingers).

Table 4.15 EASE calculations

Activity	Temperature	Contact level	Use pattern	Pattern of control	EASE conc estimate mg/cm^2/day
Manual charging	25^{o}C Mobile solid	Intermittent	Non dispersive	Direct handling	0.1-1

Summary/statement of the exposure level for sc II.3- formulation of epoxy resin

The reasonable worst case for formulation of epoxy resin is in the range 5 – 6.6 mg/m^3 and the highest measured value of 6.6 mg/m^3 is brought forward to the risk characterization as a RWC value for inhalation exposure.The highest EASE value of 420mg/day is brought forward to risk characterization as a reasonable worst case for dermal exposure.

Scenario II.4- Production of chemicals used in synthesis

A. Production of oilfield chemicals

Butylphenol/formaldehyde resins are ethoxylated to produce specialised surfactants for the separation of crude oil in aqueous refinery effluent from off-shore oil. In all these processes the resin is mixed with other resins/components and, with the exception of tyre tackifiers, further reaction takes place. This reaction will also occur with any free p-t-butylphenol in the resin. While it is common for commercial ptBP/formaldehyde resins to contain up to 3% free p-t-butylphenol, this dilution and reaction will reduce the free monomer to very low levels. Therefore, no emission of ptBP during use of the chemicals can occur since it is chemically bound in a polymer matrix. Emissions can only occur during the production of phenolic resins, which are subsequently ethoxylated.
Industry has been asked to forward more information. Occupational exposure may be similar to phenolic resin production.

B. Hydrogenation
PtBP can be hydrogenated to yield the respective alcohol, i. e. p-tert.-butylcyclohexanol. Emissions of ptBP can only occur during the hydrogenation process, but not during the use of the alcohol. The hydrogenation is done in a strictly controlled closed system under high pressure using hydrogen (highly explosive). Emissions to the environment are therefore unlikely to occur.
Industry informs that less than 10 persons are working continuously with the process and less than 50 persons are working intermittently (up to 50 % of the working hours). The process temperature is 200 ^{o} C. It is an outdoor plant with a closed process with manual handling. Residual levels in final products are less than 100ppm (detection limit was 1ppm). The final products are used both on site and for industrial use. No information about occupational exposure has been presented.

C. Use of ptBP as an intermediate for the production of a rubber additive

PtBP is used as an intermediate for the production of a rubber additive. PtBP is reacted with acetylene and the resulting polymer is used as a rubber additive. Within the rubber industry the resulting polymer is used as a tackifier (mainly for tires). The polymer is a solid material marketed in form of "pastils".
A biomonitoring (3 weeks) of ptBP was conducted at a producer in workers that work in the packaging area of the final polymer. No ptBP was detected in the urine of workers.
PtBP is delivered in molten form via trucks. The material is pumped via pipelines into the storage tank of the closed production unit (single purpose facility) (Foussereau, et al. 1982).

Summary/statement of the exposure level for sc II.4- production of chemicals used in synthesis.

Due to lack of data scenarios A, B and C are compared with scenario II.2 production of phenolic resin For the production of oil field chemicals (Scenario A) industry informs that emissions only will take place under the production of phenolic resins. In scenario C for the production of rubber additive, ptBP is used as a raw material and the working tasks may be comparable to the other formulating and processing scenarios. Industry informs that hydrogenation (Scenario B) is a strictly closed process at 200 ^{o}C, but with some manual handling, and we assume that the exposure will not be as high as for the other formulating and processing scenarios.

4.1.1.2.3 Occupational exposure from end uses

Scenario III

Scenario III.1 Use of polycarbonates

Polycarbonate is used for producing CDs, DVDs, solid and multiwall sheets in glazing applications and films, food contact containers-e.g. storage of food and beverages, tableware, medical devices, blends for use in electronic and automotive industry.

Residuals of the free monomer bound in the polymer matrix are typically not detectable to a detection limit of 5ppm.

Injection moulding is the most commonly used conversion process for the production of a variety of articles as digital versatile discs (DVD) and compact discs (CD)
Extrusion is used for conversion of polycarbonate resins into profiles, films and sheets.

Injection moulding is a conversion process where the plastic material is produced in a cyclical process. Polycarbonates are gravity-fed via a hopper to a rotary screw housed into a heated barrel. During each cycle, a defined amount of material is melted and carried forward to the tip of the screw. This material, now heated to approximately 280-350^{o}C, is then injected under pressure into the mould cavity a sealed, hollow space, where it is cooled to 80-130^{o}C until once again it is in the solid state conforming to the shape of the article. Finally the mould opens and the article is ejected.

In an occupational hygiene measurement polycarbonate resin was moulded to digital versatile discs (DVD's).
Polycarbonate is melted at 350 ^{o}C. Melted polycarbonate is injected in a hot mould of temperature 120^{o}C in a closed system. Normally the worker is separated from the process. The production line is placed in a clean room with general ventilation.

Measurements of occupational exposure were conducted with personal and fixed collection systems. The position of the fixed collection systems was beside the mould in a height covering the breathing zone of the worker displaying a worst case scenario. The mould is shielded with a contact protection glazing.

Measurements were taken when the production line where prepared and during the continuous production process. Detection limits were determined in a range of 0.2 to 1.9 µg/m^3 depending of the air volume of the specific samples.

Table 4.16 Production of DVD from polycarbonates – measured values

Activities/events	Measured values Air samples Median µg/m3 (range) (no of measurements)	95-Percentile mg/m^3 sampling period P= personal A=area	Comments
Production	<detection limit (DL) DL=0.4 (1)	P Measured period: 2 hours	Measurements done in August 2002
Production	<DL DL=0.4 (1)	A Measured period: 2 hours	Measurements done in August 2002
Preparation of the production line	<DL DL=1.6-1.9 (2)	P Measured period: 0,5 hours	Measurements done in August 2002
Preparation of the production line	<DL DL=0.9 (1)	A Measured period: 0.5 hours	Measurements done in August 2002

Extrusion of polycarbonates into single- and multi-wall sheets

The extruder is a machine used to melt the plastic and continuously deliver this melt under pressure to a die. Typically, extrusion begins with granular or flake material gravity-fed via a hopper to a rotary screw. The screw, a raised helix, traps material and moves it forward through an enclosed heated chamber, the barrel, where the polycarbonate is typically heated to 240-300 °C.
The die shapes the melt into the form of a sheet. After exit from the die, the extruded plastic is uniformly cooled down and solidified in a cooling unit. In this unit also the surface finish is provided to the sheet and the final sheet dimensions are set. Take away equipment consisting of rubber draw rolls supplies the sheet to a cutting or sawing device after which the cut sheets are collected in the stacking unit.

A local exhaust ventilation unit, consisting of a vent hood connected to an exhaust duct is usually placed above the die to effectively remove the processing fumes that are released at this point.
Polycarbonate for outdoor applications is produced as multiple layer structures whereby a second extruder extrudes a capping layer on top of the core layer. The resin used to produce the top layer is a polycarbonate containing UV stabilising additives to protect the core of the sheet.

Airborne ptBP has been determined during a sheet extrusion run using polycarbonate resins Mono-layered triple-wall sheets with a thickness of 10mm have been extruded. Polycarbonate in the form of either flake or granulate were used in the extrusion. The emissions levels have been determined at various positions in the immediate vicinity of the processing equipment and in the duct of the local exhaust ventilation system, positioned above the die. All samples were stationary. Data were conducted with detection limit 0.05ppm.

Table 4. 17 Sheet extrusion using polycarbonate resin

	Measured values Air samples Median mg/m^3 (range) (no of measurements)	95-Percentil mg/m^{3}sampling period P=personal S=stationary	Comments
Production of triple-wall sheets Different positions in the vicinity of the production equipment	< detection limit of 0.3mg/m^3 (29)	S Sampling time 10-120min	Measurements done in July 1999, Research and Developments facilities
Production of single- and multi-wall sheets	< detection limit of 0.01mg/m^3 (19)	S, P Sampling time= 50-141min.	Research and Developments facilities

New personal and stationary measurements were performed from the production site in May 2003. Multi-wall sheets with a thickness of 35 mm were extruded, and a solid single-wall sheet with a thickness of 1mm was processed. Each line was operated by one worker.
A lower detection limit of 0.01 mg/m^3 had been established. 19 samples were taken, sampling period varied from 141 to 50 minutes. The concentrations found in all samples were lower than the detection limit of 0.01 mg/m^3.

Summary/statement of the exposure level Sc III.1 using polycarbonates

The measured values with improved analytical methods are less than 0.01 mg/m^3 and this value is taken forward to the risk characterisation as a reasonable worst case for inhalation exposure. Since there will be less than 5wtppm of free monomer in the polymer matrix, dermal exposure is considered negligible. Residuals of the free monomer bound in the polymer matrix are typically not detectable to a detection limit of 0.005ppm.

Scenario III. 2 Use of phenolic resins

Phenolic resins are used in automotive applications, abrasive and refractory industry, foundry industry, surface protection, adhesives and wood based materials.
Possible leakage of ptBP from these materials has to be taken into account.

Cases of occupational allergy have been reported from use of ptBP-formaldehyde resin in the shoe-making industry. The resin was found in certain neoprene adhesives (Fossereau et al. 1982). In an epidemiological study from 5 different shoe factories, the most common occupational allergens were ptBP-formaldehyde resin. 2 workers had vitiligo-like leukodermic patches on the backs of their hands and on their forearms (Mancuso et al. 1996). Preparation and gluing in the assembly department were particulary associated with occupational allergic contact dermatitis. Neoprene-based adhesives were found to be associated with the dermatitis.

PtBP formaldehyde resins used for the production of some polychloroprene adhesives have a maximum content of free ptBP of 4% by wt. The final adhesive is an interpenetrated network (IPN) in solvent base. Since ptBP has a high solubility both in the resin and the chloroprene, the release of ptBP is not expected to be very high even during the application of the adhesive.

No occupational measurements have been presented from industry.
Shoemakers has been described as a population with possible exposure. They are assumed to be exposed when they handle uncured glues manually, intermittent and without protection. Contact with the cured glue is not expected to contribute to the exposure.

Phenolic resins are also reported to be used for roll and spray painting.

Inhalation exposure

Measured data
No measured data is available

Modelled data
EASE

Table 4.18 EASE calculations

Activity	Temp	Use pattern	Pattern of control	EASE conc if pure ptBP mg/m^3
Shoemaker handling uncured glues	25 ^{o}C liquid	Non-dispersive	Direct handling with dilution ventilation	62-310 4% ptBP in adhesive: 12 mg/m^3
Painting without aerosol formation	25 ^{o}C liquid	Wide dispersive	Direct handling with dilution ventilation	0-0.62 mg/m^3

The amount of free ptBP in the adhesive is 4% .The estimated worst case inhalation exposure is then 12 mg/m^3.

3 modelled estimates for painting with phenolic resins have been suggested:

1. EASE estimates for workers rolling paint– typical inhalation exposure.

No aerosol is formed during the working operation. The process temperature is 25 ^{0}C and the physical state of ptBP is liquid. The use is wide dispersive. The pattern-of-control is direct handling. Dilution ventilation is present. The exposure will then be in the range of 0-0.62 mg/m^3.

2. EASE estimates for workers rolling paint–worst case inhalation exposure.
Painting without aerosol formation: The process temperature is 25 ^{0}C and the physical state of ptBP is liquid. Aerosol formation will not be a problem. The use is wide dispersive. The pattern-of-control is direct handling. Ventilation is absent. The exposure will then be in the range of 0-0.62 mg/m^3.

3. Spray painting – typically inhalation exposure.
Aerosol exposure estimated from the TNO-model for paint containing 5% free ptBP = 1.7 mg/m^3. Some of the aerosolized ptBP will evaporate, but that will not change the combined exposure level of the vapour and liquid phases. However, as ptBP is semi-volatile substance some contribution from the painted surfaces will contribute. The rapporteur has not found a modell for this. The vapour pressure of ptBP at room temperature is 0.0005 mm Hg = 0.1 ppm or 0.6 mg/m^3. The maximum combined exposure to particulate and vapour phase ptBP is therefore 2.4 mg/m^3.

Dermal exposure

Measured data
No measured data is available.

Modelled data:
EASE

Table 4.19 EASE calculations

Activity	Temp	Use pattern	Pattern-of-control	Contact-level	EASE conc in glue mg/cm^2/day
Shoemaker handling uncured glues	25 ^{o}C liquid	Non-dispersive	Direct handling	Intermittent	0.1-1

As the concentration of the glue is maximum 4% the estimated exposure is 0.004-0.04 mg/ cm^2/day. Exposed surface area is supposed to be 420cm^2 (palms and fingers exposed).
This will give an estimated exposure of 1.7-17 mg/day.
If the product contains free ptBP in the region of ppm (e.g. in cured neoprene-adhesive) the exposure should be negligible.

Spraying painting

The TGD Appendix IE suggests a default value of 3 mg/cm^2, with a 4% free PtBP in the paint and and an exposed surface area of 420 cm^2, this will give an estimated exposure of 50 mg/day.

Summary/statement of the exposure level- ScIII.2 Use of phenolic resins

The calculated EASE values of 12 mg/m^3 for inhalation for a typical case exposure, and the default value of 33.6 mg/day for dermal exposure are brought forward as a reasonable worst case value for a full shift.
For spray painting the modelled reasonable worst case inhalation value of 2.4 mg/m^3 and the estimated dermal exposure of 50 mg/day are brought forward to the risk characterisation.

Scenario III.3 Use of epoxy resins

No occupational data have been presented from industry.

The amount of free ptBP is considerable in epoxy hardeners, up to 30% free ptBP. The amount of free ptBP in reactive diluents and the epoxy resin is lower <10% (see Sc II.3). Some ptBP may also leak from cured epoxy resins, but this is probably much less because the content of free ptBP is lower and high temperature cured resin is practically insoluble in water. There is some uncertainty about ambient cured resins, however**.**

No information on exposure or process has been presented by the industry. We therefore assume that the highest exposures occur during manual handling of epoxy hardeners and reactive diluents with a maximum content of free ptBP of 30%. In this scenario the worker is assumed to mix the components manually, intermittent and without protection.

Inhalation exposure

Measured data
No measured data is available

Modelled data
EASE
Table 4.20 EASE calculations

Activity	Temp	Use pattern	Pattern of control	EASE conc if pure ptBP mg/m^3
Manual handling of epoxy reactants	25 ^{o}C liquid	Non-dispersive	Direct handling with dilution ventilation	62-310

The amount of free ptBP in the reactants is 30%. The estimated reasonable worst case inhalation exposure is then 93 mg/m^3 (30ppm).

Tank spraying using epoxy resins - worst case scenario:

The industry reported that epoxy resins are used for internal spraying of tanks in ships, but no further information on this scenario has been given. The rapporteur has made a scenario with assumptions concerning the tank size and the paint: the dimensions of the tank were 10m x 10m x 10m with a volume of 1000 m^3 and a surface area of 600 m^2, the tickness of the paint film was 100 μm and the paint contained 3% of free ptBP. The exposure level estimated by the TNO model of 1 mg ptBP/m^3 probably underestimates the exposure levels grossly. A total of 60litres of paint is used to spray the surfaces of the tank which contains 3kg of free ptBP that may evaporate. Without ventilation the concentration in the tank will be at most the vapour pressure of ptBP which is 0.6 mg/m^3 at room temperature as there is enough free ptBP present. The aerosol exposure is thus the dominating phase, but estimation of this scenario was not possible. An estimate has been calculated using the TNO-model: If we assume a safety factor of 5 because the studies that the TNO-model is based on often applied ventilation, an aerosol concentration of 5 mg/m^3 is estimated and the combined exposure to vapour and aerosol is 5.6 mg/m^3. This value will be forwarded to the risk characterizartion.

Dermal exposure

Measured data
No measured data is available

Modelled data
EASE

Table 4.21 EASE calculations

Activity	Temp	Use pattern	Pattern-of-control	Contact-level	EASE conc of hardener mg/cm^2/day
Manual handling of epoxy reactants	25 °C liquid	Non-dis-persive	Direct handling	Intermittent	0.1-1

As the concentration of ptBP hardener is maximum 30% the estimated exposure is 0.03-0.3 mg/ cm^2/day. Considering fingers and both palms exposed, the surface area will be 420 cm^2. This will give an estimated exposure of 13-130 mg/day.

There is no default value for dermal exposure during spray painting in the TGD. However Marquart *et al*. (2006) presented a number of defaults values for dermal exposure including one for spray painting on large areas. This default (12000 mg full product as reasonable worst case and 3400 mg as typical value on 840 cm^2) is based on a number of data sets with reasonable worst cases between 5600 and 13600 mg. These values are all calculated from measured data on non-volatile (or very low volatility) substances.

Assumed exposed areas are both forearms (840 cm^2) with a reasonable worst case exposure of 12000 mg or 14 mg/cm^2/day. Typical total exposure is 3400 mg/day or 4 mg/cm^2 /day. For a 30% solution this will give a value of 3600 mg/day for reasonable worst case and 1020 mg/day for a typical value.

For manually handling of reactants the TGD Appendix 1 E dermal values for brushing and rolling of liquids is applied. Assumed exposed areas are both forearms (840 cm^2) with a reasonable worst case exposure of 1000 mg or 12 mg/cm^2/day. For a 30 % solution this will give a value of 3000 mg/day for reasonable worst case and 510 mg/day for a typical value. The last 510 mg/day is brought forward to the risk characterisation.

Summary/statement of the exposure level- ScIII.3 use of epoxy resins

For manually handling of reactants the calculated EASE values of 93mg/m^3 for inhalation and the default value of 510 mg/day are brought forward as a reasonable worst case value. For spraying the inside of tanks 3600 mg/day for dermal exposure are brought forward as a reasonable worst case value and 1020 mg/day for a typical value for a full shift. For tank spraying the estimated exposure of inhalation of 5.6 mg/m^3 is brought forward to the risk characterisation.

Scenario III.4 Use of rubber additive (polymer) in uncured rubber.

PtBP is used as an intermediate for the production of a rubber additive. (Scenario II.4.D). Within the rubber industry the resulting polymer is used as a tackifier (mainly for tires). The polymer is a solid material marketed in form of "pastils".

A cluster of five vitiligo cases has been reported (O'Mally et al. 1984). The five cases were diagnosed among 199 workers at a company that manufactured hydraulic pumps with rubber injection moulded interiors. PtBP and 2,4-ditertiary butylphenol were identified as probable causes for the four of the five cases. Both compounds were present in the rubber stock that was handled by the workers. The uncured rubber contained 0.01-0.03 % di-ptBP and trace amounts of ptBP. The prevalence of vitiligo was significantly increased in workers most exposed to uncured rubber. They fed uncured rubber to a mill before the rubber was injection moulded. Exposure measurements are not available.

Inhalation exposure

Measured data
No measured data is available

Modelled data
EASE

Table 4.22 EASE calculations

Activity	Temp	Use pattern	Pattern-of-control	EASE conc mg/m^3
Production worker milling uncured rubber	25 °C Mobile solid	Non-dispersive	Direct handling with dilution ventilation	62-310

Without further knowledge about rubber formulations we assume that some materials may contain 0.01-0.03 % free ptBP as several alkylated phenols can be used for this purpose. Further assumptions are that the workers handle dusty material without protection. The estimated worst case inhalation exposure is then 0.09 mg/m^3.

Dermal exposure

Measured data
No measured data is available

Modelled data

EASE

Table 4.23 EASE calculations

Activity	Temp	Use pattern	Pattern-of-control	Contact level	EASE conc uncured rubber dust mg/cm^2/day
Production worker milling uncured rubber	25 ^{o}C Mobile solid	Non-dispersive	Direct handling	Intermittent	0.1-1

The amount of free ptBP in the uncured rubber is assumed to be 0.03%. The estimated worst case dermal exposure is then 0.3 μg/m^2. Considering fingers and both palms exposed, the surface area will be 420 cm^2. This will give an estimated exposure of 0.13 mg/day.

Summary/statement of the exposure level- scenario III 4 use of uncured rubber.

The calculated EASE values of 0.09 mg/m^3 for inhalation and 0.13 mg/day for dermal exposure are brought forward as a reasonable worst case value for a full shift

4.1.1.2.4 Summary of occupational exposure

Table 4. 24 Conclusions of the occupational exposure assessment

Scenario	Activity [1]	Frequency Days/year	Duration Hours/day	Inhalation				Dermal			
				Reasonable worst case		Typical concentration		Reasonable worst case		Typical concentration	
				Unit mg/m³	Method[2]	Unit mg/m³	Method [2]	Unit mg/day	Method [2]	Unit	Method [2]
Sc 1 Production											
Production Operators											
Product packing	Full shift	Every day	8h/ pr day	0.76	Measured	0.39	Measured	Negligible Automated system			
Sampling	Short term	6X1min a day		19	EASE	7.3	Measured	Negligible (hot liq.)			
Sc 2 Formulation and Processing											
II.1 Production of polycarbonate resins											
Production	Full shift		8h/day	0.014	Measured			Negligible (hot liq.)			
operators											
Unloading ptBP from ISO tanks	Short Term	2-3 times a week	1-1.5 h/day	0.6	EASE	0.11	Measured	Negligible (hot liq.)			
II.2 Production of phenolic resins, Production of chemicals used in synthesis											
Production	Full shift		8h/day	0.6	EASE			Negligible (hot liq.)			
II.3 Production of epoxy resins											
Formulation		1 h /day		6.6	Measured, personal			420	EASE		

Sc 3 End use scenarios											
III.1 Use of polycarbonate	Full time			< 0.01	Measured			Negligible (hot liq.)			
III.2 Use of phenolic resin. Handling uncured glue	Full time	Every day		12	EASE dilution			33.6	Default value, dilution		
III.2 Use of phenolic resins. Spray painting.	Full time	Every day		2.4	TNO			50	TGD Appendix 1E		
III.3 Use of epoxy resin. Manually handling of reactants	Full time	Every day		93	EASE dilution			510	Default value, dilution		
III.3 Use of epoxy resins. Tank spraying.	Full time	Every day		5.6	TNO			3600	Default value, Marquart	1020	Default value, Marquart
III.4 Use of rubber addiitive in uncured rubber	Full time	Every day		0.09	EASE dilution			0.13	EASE, dilution		

1: Full shift, short term, etc. 2: Measured, EASE, Expert judgment, Calculated, etc.

4.1.1.3 Consumer exposure

4.1.1.3.1 Exposure from uses

Consumer exposure is possible via direct use of products with phenolic resins or epoxy resins containing residual ptBP monomers, or via use of the final articles containing residual concentrations of ptBP. According to information in the Norwegian Product Register (2003) consumer use has been identified for the product types adhesives, paints and varnishes (cf. chapter 4.1.1.1). Consumer exposure is furthermore possible via the use of products made of polycarbonates such as containers for storage of food and tableware.

Butylphenol/formaldehyde resins (ptBP-FR) are used in contact and pressure sensitive adhesives and coatings. According to industry the residual concentration of free ptBP in ptBP/formaldehyde resins has been determined to be in the range of 0.5 – 3 %, varies from batch to batch and between resin types. The residual concentration of ptBP in resins for tackifiers was stated to be less than 5%.

According to information in the Norwegian Product Register (NPR) the concentration of ptBP in adhesives are generally very low (from 0.1 to 1 %). Direct use of such adhesives by consumers would potentially give rise to exposure to ptBP. In earlier drafts of the risk assessment report of ptBP a much higher consentration of ptBP was given in the declarations to NPR but this has been corrected so that it is differentiated between total and residual free monomer As a worst case scenario a concentration of 1 % residual ptBP in adhesives for consumers will be used in the risk characterisation.

The concentration of residual monomers is likely to be reduced during production of the articles, and generally low residual concentrations of ptBP are present in the final articles. The residual concentrations of non-reacted ptBP in polycarbonate have been measured. The concentration was found to be non-detectable, at a limit of detection of 5 ppm.

PtBP formaldehyde resin (ptBP-FR) is also used in adhesives for the surfaces of leather and rubber due to its good binding qualities and tackiness.

PtBP resins are also used in paints, varnishes and lacquers. According to the information in the Norwegian Product Register consumer use has been identified for the product types “paints and varnishes, active corrosion inhibitor” (solvent based) and “paints and varnishes, decorative/protection” (solvent based). The concentration of ptBP in paint and lacquer products for which consumer uses are indicated seems generally to be low (< 1 %).

In general, high temperature cured epoxy formulations are not expected to release significant amounts of ptBP. This applies especially for can coatings, where food approval requirements have to be fulfilled. An upper limit (according Directive 2002/72/EC) of 50 μg/kg food has been decided.

However ambient cured epoxies can be expected to have a significantly lower level of true-cure than epoxies cured at high temperatures and more data on potential release of ptBP is needed.

Epoxy-based paints/coatings can be used for drinking water reservoirs that are frequently used on ships and offshore installations. CEPE has informed that none of the CEPE members use ptBP either in food contact or in portable water reservoirs. However, products for such use were identified only few years ago and it therefore seems reasonable to keep the scenarios as this use can not be completely ruled out. The products may contain significant amount of free ptBP. Potential exposure to ptBP via drinking water is therefore considered. According to German guidelines ("Leitlinie zur hygienischen Beurteilungen von Epoxidharzbeschichtungen im Kontakt mit Trinkwasser") ptBP is included in the "Positive list" with a corresponding provisional limit value in drinking water of 2.5 μg/l.

It has been reported that ptBP has been detected in drinking water from pipelines of polyethylene.

According to literature ptBP-FR is also used in motor oil additives, insulation, fiberglass, furniture, disinfectants, deodorants, inks, film developers, cosmetics and dental bonding materials. In addition ptBP is used as an antioxidant in rubber and in plastic material for eyeglass frames. Other equipment made of cellulose ester plastics that might contain ptBP, as an antioxidant to prevent discoloration and inhibit photo-oxidation, are hearing aids, tooth and hair brush handles, tool handles, toys and other tough, transparent plastics which often come in contact with the skin for prolonged periods. The amount of ptBP in these consumer products varies and is seldom known.

In a study by Ozaki and Baba (2003) levels of ptBP, other alkylphenols, and bisphenol A (BPA) were measured in 60 randomly selected rubber products in food contact use (33 samples), infant related use (13 samples) and other uses (14 samples). Samples were cut into small pieces, and 1 gram was steeped for 24 hours in 10 ml aceton maintained at 40 ^{o}C, after which it was evaporated and the residue dissolved in n-hexane. Finally the test solution was made up to 2 ml with acetone and subjected to GC/MA analysis. Due to the use of cutting edges, this study can be regarded as a worst case scenario. PtBP and BPA were not found in any sample. The detection limit was 2.0 μg/g.

For consumer exposure four main possible exposure scenarios have been identified.

I. Exposure from direct consumer use of adhesives containing ptBP

II. Exposure to ptBP in drinking water from drinking water reservoirs and pipelines

III. Exposure to ptBP from polycarbonate used for food contact applications

IV. Exposure to ptBP from epoxy resins used for canned food

Dermal exposure is considered the main exposure route for ptBP in phenolic formaldehyde resins, whereas oral exposure is the main exposure route for ptBP in polycarbonate used for food contact applications and drinking water reservoirs/pipelines and canned food. For glue there are two subscenarios – use of small amounts of superglue and use of larger amounts of universal glue.

Scenario Ii: Exposure from direct consumer use of small amounts of adhesives (Superglue) containing ptBP

Dermal exposure

Measured data

According to information in the Norwegian Product Register (2003) the residual concentration of ptBP in adhesives is generally low (0.1 to 1%). As a worst case scenario a concentration at 1 % ptBP in adhesives will be used in the risk characterisation.

Skin of finger and hands is assumed to be exposed to approximately 0.5 % of the used adhesive (RAR on Toluene, 29.07.2003; Bremer and Veen, 1999). The dermal external exposure to ptBP from adhesives is then: 500 mg adhesive x 1 % x 0.5 % x 1/ (70 kg bw) = 0.00036 mg/kg bw/event. The frequency of use of this scenario is estimated to be once a week. Since the toxicokinetic studies indicated that ptBP is rapidly excreted, an acute time scale is considered appropriate. The value of 0.00036 mg/kg bw/event will be put forward to the risk characterisation scenario Ii. An estimated daily intake would then be 0.00036 mg/kg bw divided by 7 days that gives a daily exposure estimate at 0.000051 mg/kg/day. The value of 0.00036 mg/kg bw and 0.000051 mg/kg/day will be put forward to the risk characterisation scenario Ii.

Scenario Iii: Exposure from direct consumer use of larger amounts of adhesives (Universal glue) containing ptBP

Dermal exposure

Measured data

According to information in the Norwegian Product Register (2003) the residual concentration of ptBP in adhesives is generally low (0.1 to 1%). As a worst case scenario a concentration at 1 % ptBP in adhesives will be used in the risk characterisation.

In the estimation of dermal exposure we assume that the amount of adhesive binding to a specific surface area is approximately 59 mg/cm^2 (representing the area of two hands) of the used adhesive (RAR on Bisphenol-A, 08.10.2003; Hansen, Paul Lyck et al., 2008). In order to assess the area of skin of fingers and palms that will be exposed to adhesives it is assumed that 2 % (17 cm^2) of the total surface area will get in contact with the adhesive, and there is a content of 1% ptBP in the adhesive, it will result in the following exposure to ptBP:
(59mg/cm^2 * 840 cm^2 * 0.02 * 0.01)/70 kg bw = 0.142 mg/kg bw/event (840 cm^2 represents the total surface area of two hands). The value of 0.142 mg/kg bw/event will be put forward to the risk characterisation scenario Iii. The frequency of exposure was estimated to be once a week. An estimated daily intake would then be 0.142 mg/kg bw divided by 7 days that gives a daily exposure estimate at 0.0203 mg/kg/day. The value of 0.142 mg/kg bw and 0.0203 mg/kg/day will be put forward to the risk characterisation scenario Iii.

The footwear depigmentation related to adhesives used in shoemaking was found to be most common in tropical countries outside EU (Bajaj et al., 1996), and is therefore not considered as a relevant scenario in the risk characterisation for consumers in EU-countries. Therefore, no exposure assessment was made for this scenario.

Scenario II: Exposure to ptBP in drinking water from drinking water reservoirs and pipelines

Oral exposure

Measured data

Epoxy-based paints/coatings are used for drinking water reservoirs frequently used on ships and offshore installations. However, not all epoxy-based paints/coatings contain ptBP. According to the Norwegian Product Register (1999) the concentration of ptBP in epoxy-based paints/coatings used for drinking water reservoirs is up to 1 - 5 % after mixing the two components of the product. Potential exposure to ptBP should therefore be considered. Under experimental conditions plates coated with epoxy-based paint containing ptBP were put in water reservoirs. The levels of ptBP measured in water after 9 days were < 0.02 μg/l water. The procedure for curing had been fulfilled for these plates. The daily intake of ptBP using the detection limit of the measurments in water from drinking water reservoirs with epoxy-based paints/coatings can be calculated: 0.02 μg/l x 2 l/day x 1/(70 kg bw) = 0.00057 μg/kg bw/day (when TGD values of daily water intake at 2 l/day and a bw of 70 kg are used).

The procedure for curing related to the use in water reservoirs is very extensive (high temperature, washing and long ventilation time). In general high temperature cured epoxy formulations are not expected to release significant amounts of ptBP. However, the curing procedure may not always be adequately followed, and a higher release of ptBP may then be expected. As a worst case scenario it is assumed that 10 times more ptBP may be released into the water from drinking water reservoirs with epoxy-based paints/coatings. This would lead to a daily external intake of:

0.2 μg/l x 2 l/day x 1/(70 kg bw) = 0.0057 μg/kg bw/day. This value will be taken forward to the risk characterisation.

In a study by Brocca et al., 2002 the level of phenol derivatives was studied in drinking water from piplines of polyethylene. Chemical analysis of drinking water from the pipelines showed that a small amount, up to 6.6 μg/l of ptBP was released from the pipelines to the drinking water after a 7 days migration test. Since the duration of the migration test was 7 days 6.6 μg/l is divided with 7. According to TGD the daily intake of water is 2 l/day and the bw 70 kg. The measured external exposure level of ptBP in water from pipelines is therefore as follows:

6.6 μg/l/7 x 2 l/day x 1/(70 kg bw) = 0.027 μg/kg bw/day. This value will be taken forward to the risk characterisation.

In summary, the consumer exposure to ptBP from water reservoirs is 0.0057 μg/kg bw/day) and from pipelines is 0.027 μg/kg bw/day. These values will be taken forward to the risk characterisation.

Scenario III: Exposure to ptBP from Polycarbonate used for food contact applications

Measured data

Oral exposure

Potential consumer exposure to ptBP from polycarbonate uses may arise from these applications that involve direct contact with foodstuff, as a result of migration of residual ptBP into the food.

According to EU-Directive 2002/72/EC regarding plastics intended to come in contact with food, ptBP is allowed to be used as a monomer for the production of food-contact plastics, with a specific migration limit (SML) of 50 microgram / kg food.

The migration of ptBP from polycarbonate in food contact applications has been studied using food-simulating solvents. Migration was non-detectable applying a limit of detection ranging from 6 – 16 microgram / kg food for ptBP as detailed in the tables below.

Table 4.25 Migration of ptBP

Food Simulant	Time	Temperature	microgram/kg food
Ethanol (15% v/v)	10 days	40 °C	<10*
Acetic acid (3% w/v)	10 days	40 °C	<10*
HB 307	10 days	40 °C	<10*
HB 307	30 min	121 °C	< 10*

* = detection limit
Ref.: data supplied by company A

Table 4.26 Migration of ptBP

Food Simulant	Time	Temperature	microgram/kg food
Water	10 days	40 °C	< 7 *
Ethanol (15% v/v)	10 days	40 °C	< 6 *
Acetic acid (3% w/v)	10 days	40 °C	< 7 *
Sunflower oil	10 days	40 °C	<16*

*= detection limit
Ref. data supplied by Company B

The migration of BPA and butylphenol from polycarbonate in food contact applications has been investigated. In these studies the levels of BPA in food were below the detection limit (between 0.5 to 10 μg/kg food). However, in these studies the exposure time was much lower (30 min) compared to up to 10 hours for the data of ptBP levels supplied by company A and B.

Table 4.27 Migration of BPA and butylphelhenol

Food Simulant	Time	Temperature	Microgram/kg food
[a]Acetic acid (4 % w/v)	30 min	60 ^{0}C	< 0.5*
[b]Water	30 min	95 ^{0}C	< 10*
[b]Water	30 min	60 ^{0}C	< 10*
[b]Ethanol (20 % v/v)	30 min	60 ^{0}C	< 10*
[b]Acetic acid (4% w/v)	30 min	60 ^{0}C	< 10*
[b]Acetic acid (4% w/v)	30 min	95 ^{0}C	< 10*
[c]Water	30 min	60 ^{0}C	< 5*
[c]Ethanol (20 % v/v)	30 min	60 ^{0}C	< 5*
[c]Acetic acid (4% w/v)	30 min	60 ^{0}C	< 5*

[c]n-Heptan	30 min	60 ^{0}C	< 5*

* = detection limit
[a]Kitagawa et al., 1999
[b]Yotoriyama et al., 1999
[c]Sugita et al., 1994

In the risk characterisation the detection limit at 16 μg/kg food for migration of ptBP from polycarbonate in food contact applications will be used.

The total daily intake of food and drinking water for a consumer is approximately 5 kg (2 l drinking water and 3 kg food (TGD values) of which 1 kg food is considered to be in contact with polycarbonate containing material. If the 1 kg food were of different types, and thus divided into many small packages (e.g. many different kinds of cheeses) the surface area of the packaging material would increase and the emissions of ptBP into the food as well. Polycarbonate bottles may contain ptBP, however, according to industry ptBP is not considered used in polycarbonate used for drinking bottles. Exposure from drinking water from polycarbonate bottles is therefore not included. The external exposure to ptBP from food contact applications is calculated to be: 16 μg/kg food x 1 kg food x 1/(70 kg bw) = 0.23 μg/kg bw/day. This value will be taken forward to the risk characterisation.

Scenario IV: Exposure to ptBP from epoxy resins used for canned food.

The estimated external uptake of ptBP from canned food based on an SML of 50 μg/kg food and a food intake of one kg/day would be: 50 μg x 1 kg food x 1/70 kg bw) = 0.71 μg/kg bw/day. This exposure estimate is based on the specific migration limit given in Directive 2002/72/EC of 50 μg/kg food. This is the maximum dose a consumer may be exposed to from canned food.

4.1.1.3.2 Summary of consumer exposure

For consumer exposure four main exposure scenarios have been identified. The dermal exposure in scenario Ii, external exposure from direct consumer use of adhesives (superglue) containing ptBP was calculated to be 0.051 μg/kg bw/day and Iii, external exposure from direct consumer use of adhesives (Universal glue) containing ptBP was calculated to be 0.0203 mg/kg bw/day. The daily intake of ptBP in scenario 2, exposure to ptBP in drinking water from drinking water reservoirs and pipelines was calculated to be 0.0057 μg/ kg bw/day and 0.027 μg/ kg bw/day, respectively. The external intake of ptBP in scenario 3, exposure to ptBP from polycarbonate used for food contact applications was calculated to be 0.23 μg/ kg bw/day. In scenario IV, exposure to ptBP from epoxy resins used for canned food the external exposure was calculated to be 0.71 μg/kg bw/day. These external exposure values will be taken forward to the risk characterisation.

4.1.1.4 Humans exposed via the environment

According to the scenarios described in the environmental section 3.1.1 the human intake of ptBP for local scenarios from production of phenolic resins and epoxy resins has been estimated by EUSES and is described in table 4.28 as well as the local exposure from production site B and from production of polycarbonate. The regional exposure scenario estimated by EUSES is also presented in the same table.

Table 4.28 Estmated human intake of ptBP in mg/kg/bw/day through environmental exposure for local site specific scenarios and local and regional scenarios as estimated by EUSES (TGD).

Scenarios[a]	Water µg/l	Soil mg/kg	Air mg/m^3	Total human intake in mg/kg bw/day
Production site B	0.11	0.10	2.14×10^{-4}	2.3×10^{-3}
Production of polycarbonates				
Site A	0.10	-	-	
Site B	0.10	-	-	
Site C	0.09	-	-	
Production of phenolic resins				
Site specific	0.66	-	-	
Generic, TGD calculation	177	1.11	1.14×10^{-5}	0.0403
Production of epoxy resins				
Sub-scenario 1 TGD calculation	771	4.83	2.8×10^{-6}	0.073
Sub-scenario 2+3 TGD calculation	2.02	0.015	5.7×10^{-3}	0.038
Sub-scenario 4 TGD calculation	193	1.21	5.2×10^{-7}	0.016
Regional	0.095	4.5×10^{-5}	7.5×10^{-7}	2.7×10^{-5}

[a]Refers to the scenarios described in section 3.1.

It can be seen that the daily human intake via the environment based upon typical human consumption and inhalation rates at the regional level is 2.7 x 10^{-5} mg/kg bw/day, and the highest local exposure scenario (epoxy resins production) is 0.073 mg/kg bw/day. This high exposure (from epoxy resins production) is related to ptBP released to water from epoxy resins production and taken up by fish and root crops (see table 4.29a and 4.29b). The regional exposure level at 2.7 x 10^{-5} mg/kg bw/day and the local exposure level at 0.073 mg/kg bw/day will be taken forward to the risk characterisation.

Table 4.29a Estimated human intake of ptBP in mg/kg bw/day from air, drinking water, fish, leaf crops, root crops, meat and milk for local site specific scenarios and local and regional scenarios as estimated by EUSES (TGD).

Scenarios[a]	Drinking	Air	Fish	Leaf	Root	Meat	Milk	Total

	water			**crops**	**crops**			
Production site B	$1.7x10^{-4}$	$6.1x10^{-5}$	$2.2x10^{-5}$	$1.4x10^{-3}$	$6.5x10^{-4}$	$1.2x10^{-6}$	$7.2x10^{-7}$	$2.3x10^{-3}$
Production of polycarbonates								
Site A	-	-	-	-	-	-	-	-
Site B	-	-	-	-	-	-	-	-
Site C	-	-	-	-	-	-	-	-
Production of phenolic resins								
Site specific	-	-	-	-	-	-	-	-
Generic, TGD calculation	$4.2x10^{-3}$	$3.5x10^{-6}$	0.029	$3.7x10^{-4}$	$7x10^{-3}$	$1.9x10^{-6}$	$1.1x10^{-6}$	0.0403
Production of epoxy resins								
Sub-scenario 1 TGD calculation	$8x10^{-3}$	$1x10^{-6}$	0.033	$1.3x10^{-3}$	0.031	$3.8x10^{-6}$	$2.2x10^{-6}$	0.073
Sub-scenario 2+3 TGD calculation	$2.9x10^{-5}$	$1.6x10^{-3}$	$6x10^{-5}$	0.036	$1.1x10^{-4}$	$3x10^{-5}$	$1.8x10^{-5}$	0.038
Sub-scenario 4 TGD calculation	$2x10^{-3}$	$3.6x10^{-7}$	$6.3x10^{-3}$	$3.2x10^{-4}$	$7.7x10^{-3}$	$9.5x10^{-7}$	$5.6x10^{-7}$	0.016
Regional	**$2.7x10^{-6}$**	**$2.2x10^{-7}$**	**$1.9x10^{-5}$**	**$4.8x10^{-6}$**	**$4.7x10^{-7}$**	**$5.1x10^{-9}$**	**$3x10^{-9}$**	**$2.7x10^{-5}$**

[a] Refers to the scenarios described in section 3.1.

Table 4.29b The estimated concentrations of ptBP in air, drinking water, fish, leaf crops, root crops, meat and milk for local site specific scenarios and local and regional scenarios as estimated by EUSES (TGD).

Scenarios[a]	**Drinking water µg/l**	**Air µg/m^3**	**Fish µg/kg**	**Leaf crops µg/kg**	**Root crops µg/kg**	**Meat µg/kg**	**Milk µg/l**	
Production site B	5.92	0.21	13.1	80.9	118	0.28	0.09	
Production of polycarbonates								
Site A								
Site B								
Site C								
Production of phenolic resins								
Site specific								
Generic, TGD calculation	146	0.011	17,500	21.4	1,280	0.44	0.14	
Production of epoxy resins								
Sub-scenario 1 TGD calculation	279	$2.8x10^{-3}$	20,300	74.7	5,580	0.88	0.28	
Sub-scenario 2+3 TGD calculation	1.0	5.71	36.7	2,110	20	7.02	2.22	
Sub-scenario 4 TGD calculation	69.7	$5.2x10^{-4}$	3,810	18.8	1,390	0.22	0.07	
Regional	**0.09**	**$7.5x10^{-4}$**	**11.4**	**0.28**	**0.09**	**$1.2x10^{-3}$**	**$3.7x10^{-4}$**	

[a] Refers to the scenarios described in section 3.1.

4.1.1.5 Combined exposure

Humans may be exposed to ptBP via direct use of products with phenolic resins or epoxy resins containing residual ptBP monomers, or via the use of the final product containing residual concentrations of ptBP. Human exposure is further possible via intake of food or drinking water contaminated from products made of polycarbonates such as containers for storage of food and tableware and exposure indirectly via the environment. The combined exposure to ptBP is the sum of all the specific sources (occupational exposure, consumer exposure, and indirectly exposure via the environment), and by all routes of exposure (oral, dermal and inhalation). However, since occupational exposure values will totally dominate the exposure levels (workers: Inhalation exposure (internal) at production: epoxy resins 0.94 mg/kg/day; phenolic resins 0.09 mg/kg/day, during end use: epoxy resins 13.3 mg/kg/day; phenolic resins 1.7 mg/kg/day), it is not considered relevant to make a separate calculation for combined exposure including occupational exposure. In table 4.30 the combined local and regional exposure to ptBP is given.

Table 4.30 Combined consumer exposure and regional and local exposure to ptBP [b] (occupational exposure to ptBP not included).

Scenario	Daily intake mg/kg bw/day
Ii Adhesives containing ptBP (super glue)	0.000051
Iii Adhesives containing ptBP (universal glue)	0.0203
II Drinking water reservoirs and pipelines	0.000033
III Polycarbonate used for food contact applications	0.00023
IV Epoxy resins used for canned food	0.00071
Local exposure[a]	0.073
Regional exposure	0.000027
Combined local[a]	**0.074[c]/0.094[d]**
Combined regional	**0.0011[c]/0.0211[d]**

[a] Highest excposure scenario for local exposure (epoxy resin production)
[b] Workers: Inhalation exposure (internal) at production: epoxy resins 0.94 mg/kg/day; phenolic resins 0.09 mg/kg/day. End use: epoxy resins 13.3 mg/kg/day; Phenolic resins 1.7 mg/kg/day
[c] Included scenario Ii.
[d] Included scenario Iii.

4.1.2 Effects assessment: Hazard identification and dose (concentration) - response (effect) assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

No data from toxicokinetic studies according to OECD 417 are available. However, the elimination of ptBP in urine and faeces was studied *in vivo* in rats (Freitag et al., 1982) as well as the the role of sulfation and glucuronidation in the biotransformation of ptBP *in vivo* in rats and in hepatocytes *in vitro* (Koster et *al*., 1981).

Oral

The excretion of ptBP via feces and urine as well as the retention of the material in certain tissues was assessed in three male Wistar rats (Freitag et *al*., 1982. U- ^{14}C-labelled material (147 µg/kg bw/day) was administered via gavage once daily for three days. The vehicle used was 0.2 % aqueous Keltron solution. Urine and feces were collected daily. The concentrations in tissues were determined after 7 days. 26.7% and 72.9% of the applied dose was eliminated via feces and urine, respectively. No radioactivity was found in adipose tissue and lung (< 0.01%) and 0.02% and 0.1% in liver and carcass, respectively. The retention of ptBP in rats after 7 days expressed as % radioactivity is given as 0.1% and can therefore be regarded as negligible. The excretion ratio (fecal excretion divided by urinary excretion) was 0.4. No information regarding metabolites identified in the exreted products, or if any parent compound was identified in the excreted products was given.

Other routes

Radiolabelled test substance, ^{14}C-labeled ptBP was injected intravenously in male Wistar rats (body weight 200 g, 4 animals/dose), dissolved in aqueous saline (pH adjusted to 10.5 by sodium hydroxide before dilution with saline) at concentrations of 1.2 – 10.34 mg/kg bw, or 8, 15, 28 and 68 µmol/kg (single dose). Bile and urine were collected subsequently for 4 hours, only one collection time.

Between 65-71% and 17-21% of the applied dose were excreted as glucuronide and sufate conjugates, respectively. (At 8, 15, 28 and 69 µmol/kg the excretion of Glucuronide was 68 ± 7, 65 ± 4, 71 ± 3 and 67 ± 3, respectively. At 8, 15, 28 and 69 µmol/kg the excretion of Sulphate was 21 ±8, 29 ± 4, 17 ± 3, and 29 ± 4, respectively). No information regarding the recovery of the parent compound in the urine or bile was given. The only information given was that no other radioactive spots other than the glucoronide and sulphate conjungates were found in bile and urine on the thin layer chromatography plates. Without further specifications

the total recovery of radioactivity was found to be 91-93% (Koster et *al*., 1981). Due to the intravenous application this study cannot be used for estimation of absorptionfigures.

In vitro studies

Koster et al., 1981 studied the sulphatation and glucuronidation of ptBP in isolated hepatocytes. In this study heaptocytes incubated with radiolabeled material for 1 hour supported the results of the *in vivo*-study.The hepatocytes conjungated the substances completely within a few minutes at the low concentration (25 μM) and within 40 minutes at the high concentration (80 μM). A slower and incomplete conjungation was found at the highest concentration probably due to toxic effects of ptBP. PtBP was mainly glucuronidated over the entire concentration range tested (25 – 800 μM), and no concentration depended shift in the ration between sulphatation and glucuronidation was reported.

4.1.2.1.2 Studies in humans

In vivo studies

Inhalation

In a biomonitoring study the urinary metabolite levels (hydrolysed sulphate and glucuronide conjungates of ptBP) in workers handling ptBP was measured as an index of personal exposure (Kosaka et *al*., 1989). It is assumed that absorption for inhalation exposure is 100 % based on the absorption percentage of 100 % for phenol (Ohtsuji and Ikeda, 1972) and on the analytical result that most of the urinary ptBP was excreted within 24 hours. The geometrical mean of eight-hour-time-weighted-average (8 h-TWA) value for personal ambient ptBP level of the packers was 0.39 mg/m^3 (*n*=15),and for carriers 0.10 mg/m^3 (*n* = 5).. The urine excreted during the latter half of the shift showed the highest levels of ptBP (geometric mean: packer, 5.07 μg/ml, *n* = 20; carrier, 3.03 μg/ml, *n* = 8). When the workers were away from the workplace ptBP levels decreased, and most were excreted within 24 hours. The total amount of urinary ptBP excreted for 24 hours after the start of the shift were two to three times higher than the estimated respiratory absorption of ptBP; ptBP was assumed to be absorbed not only through the respiratory tract but also through intact skin.

In a second biomonitoring study the urinary metabolite levels (hydrolysed sulphate and glucuronide conjungates of ptBP) in workers handling ptBP was also measured by Ikeda et *al*., 1978. Urine samples were collected from plant operators, engineers and product packers in a ptBP producing plant. No information was given regarding the exposure levels in the air to which the workers were exposed. Samples were taken during the on-duty period and also when they were off the job until they returned to the workshop on the next shift. The urinary metabolite levels of plant operators on duty were 1.2 μg/ml (0.5 – 3.0, *n* = 11), for engineers on duty 0.5 μg/ml (0.2 – 1.2, *n* = 7) and for product packers on duty 6.3 μg/ml (1.8 – 21.7, *n* = 9). The urinary metabolites of plant operators away from the work till the next shift were 0.6 μg/ml (n.d – 6.0 *n* = 10), for engineers away from the work till the next shift was below detection limit (nd – 0.4, *n* = 5) and for product packers away from the work till the next shift was 3.5 μg/ml (1.0 – 12.1, *n* = 9). The authors noted that urine levels not only reflected inhalatory uptake of ptBP, but also for a substantial part its dermal uptake.

Dermal

As regards dermal exposure to ptBP, see the human biomonitoring studies in the inhalation section, since in these studies skin penetration was also described to play an important role as a route of entry in addition to inhalation.

Oral

In vitro studies

In a study by Temellini et *al*., 1991 the structure-activity relationship of sulfotransferase and glucuronyltransferase with phenolic compounds including ptBP was studied. With the "structure-activity-relationship" it is ment that different compounds (substrates, phenolic chemicals) are substrates for glucoronide and sulphate, however, these two enzymes may contribute to the conjungation of the same substrate, but their contribution is substrate depended. PtBP was tested for enzyme kinetics in dilutions from 1mM to 0.01 µM – in 6 concentrations in duplicate. Human hepatic sulphotransferase and glucoronyltransferase was tested separate in liver cytosols and microsomal protein, repsectively.No information regarding alterations in metabolism seen at the higher concentrations was given. The kinetic parameters of the sulphotransferase in human liver for ptBP were K_m 110±32.5 µM and V_{max} 0.58±0.42 nmol min^{-1} mg^{-1}. The kinetic parameters of glucuronyltransferase in human liver were K_m 0.03 ±0.01 µM and V_{max} 4.08±0.53 nmol min^{-1} mg^{-1}. The study showed that the K_m and V_{max} of human liver UDP-glucuronosyltransferase and sulphotransferase measured for phenolic substrates were influenced by the position of the substituent in the phenol molecule and also by its chemical nature. Para-substituted phenols was shown to have a higher V_{max} for glucuronyltransferase than ortho-substituted ones. UDP-glucuronosyltransferase was shown to be less influenced than sulphotransferase by the chemical nature of the substrate since the V_{max}/K_m for glucuronyltransferase varied only over a 25-fold range, whereas the V_{max}/K_m for sulphotransferases ranged over 14000-fold for phenolic substrates.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

No data from toxicokinetic studies according to OECD 417 are available. However, the role of sulfatation and glucuronidation in the biotransformation of ptBP was assessed *in vivo* in rats as well as *in vitro* in rats and humans. The urinary metabolite levels in workers handling ptBP were also measured.

The excretion of ptBP via feces and urine as well as the retention of the material in certain tissues was assessed in rats exposed to ptBP by the oral route. The results showed that 26.7% and 72.9% of the applied dose were eliminated via feces and urine, respectively. In another *in vivo* rat study where ptBP was injected intravenously 65 – 71% and 17 – 21% of the intravenously applied dose were excreted as glucuronide and sulphate conjungates, respectively. The total recovery of radioactivity was 91 – 93 %. The *in vitro* studies with rat hepatocytes and the human liver supported the results of the *in vivo* rat study with intravenoulsy applied ptBP. The results of the rat studies where the retention of ptBP after 7 days was 0.1% can be regarded as negligible, and the likelihood for bioaccumulation is low. This is further supported by the physiochemical properties of ptBP (water solubility (600

mg/l), $logP_{ow}$ value at 3.31 and low molecular weight 152) which indicates that the likelihood for bioaccumulation is low.

The urinary metabolite levels in workers handling ptBP showed an increasing level of ptBP metabolites in the urine with increasing exposure to ptBP. Most of the ptBP was shown to be excreted within 24 hours. The studies indicated that skin penetration plays an important role as a route of entry in addition to vapour exposure.

In the risk characterisation, 100% absorption is used for oral exposure. This is based on the study by Freitag et al., where 26.7% and 72.9% of the orally applied dose were eliminated via feces and urine, respectively. In this study there was no information whether the faeces derived radioactivity stems from metabolites or unabsorbed ptBP. However, in the study by Koster et al., 1981 nearly 100 % of the intravenous applied dose was excreted as conjugated metabolites, it is not known how much of the dose that was excreted in the bile and how much was excreted via urine. Therefore, this study as such cannot be used for estimation of absorption figures. Furthermore, absorption of nearly 100 % is expected since ptBP has a low molecular weight (152), low Kow value (3.31) and high solubility in water (600 mg/l).In the absence of data on the percentage absorption by inhalation, a default value of 100 % is used for inhalation exposure. For dermal exposure no studies are available, however, related to the water solubility (600 mg/l), a $logP_{ow}$ value at 3.31 and low molecular weight (152) for ptBP an absorption of 100% is considered used for ptBP (according to the criteria in the TGD, Appendix IV, p. 263).

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

In vivo studies

Inhalation

No acute inhalation toxicity study fulfilling current guidelines is available. However, the limit test described below indicates that ptBP has low acute, systemic toxicity following inhalation (LC_{50} above 5000 mg/m^3).

A limit test has been performed, in which five male and five female rats (Sprague-Dawley) were exposed in a 120 liter chamber for 4 hours to ptBP as dust aerosol of 5600 mg/m^3 (median particle diameter of 3.6 µm) with additional vapour component of 30 mg/m^3 (Klonne et *al*., 1988). Dust aerosol was generated by leading vapour from melted ptBP (110 °C) to the exposure chamber where the vapour condenced in air to fine powder. Clinical signs observed on the day of exposure and up to 7 days postexposure included signs of mucosal irritation (perinasal, perioral, and periocular encrustation) and signs of respiratory distress (audible respiration, gasping, and a deceased respiration rate). No further details on severity of clincal signs of toxicity or number of animals affected is given in the report. Within one to two days following exposure, 1 rat of each sex died. The dead animals showed dark red or purple discoloration of the lungs and/or kidneys. No macroscopic lesions were observed in the survivors.

Two studies report that no lethality is produced by exposing rats to an atmosphere saturated with ptBP for 6 hours (Klonne et al., 1988/UCC 1985) and for 8 hours (BASF, 1971). In the former study 5 male and 5 female Sprague-Dawley rats were exposed in a chamber were 100g ptBP had been placed for 18h prior to introduction of the animal. There were no effect on body weight and no signs of toxicity following clinical observation and necropsy.

Dermal

The acute dermal toxicity of ptBP appears to be low. Two rabbit studies are reported which gives LD_{50} values above 2000 mg/kg bw. However, the LD_{50} values reported are very different. One guinea pig study with exposure of 10% solutions of ptBT indicates a LD_{50} value above 2000 mg/kg bw.

In the first dermal study ground ptBP was moistened with distilled water and applied to the clipped skin of 5 male and 5 female New Zealand rabbits at 2000, 8000, and 16.000 mg/kg bw (Klonne et *al*., 1988/UCC 1985). PtBP remained in contact with the skin for 24 h under occlusive conditions. Signs of toxicity included reduced body weight gain in the middle and high dose groups and skin irritation. In one female rabbit prostration was observed at 16.000 mg/kg bw. No lethality was observed in this study. Severe skin irritation was noted in both sexes of all treatment groups. A further description of induced irritation is given in chapter 4.1.2.3.

In the second study a dermal LD_{50} of 2.52 ml/kg bw (value given in IUCLID is 2318 mg/kg bw) for ptBP in rabbits is given in a list summarising range-finding toxicity data (Smyth et *al*., 1969). Smyth, 1969 refers to an earlier report (Smyth, 1962) for description of experimental procedures. In the 1962 report it is stated that four male albino New Zealand rabbits were used. The substance was applied to clipped trunk and retained for 24 hours beneath an impervious plastic film. No further information on the administration protocol is given. The study was said to follow a modified Draize method. The animals were observed for a 14-day period. No information on skin reactions or systemic toxicity apart from the LD_{50} values is given.

In another study a single dose of 10% ptBP solutions in olive oil or in alcohol was applied to clipped bellies of guinea pigs (The Dow Chemical Company, referred to in OECD-SIDS 2003). With the oil solution no deaths were observed at doses up to 2000 mg/kg bw, whereas the alcohol solution induced death in 1 of 5 animals at 2000 and 3000 mg/kg bw implicating a dermal LD_{50} above 2000 mg/kg bw.

Oral

In the majority of the studies reported the LD_{50} values in rats are above 2000 mg/kg bw. One rat study reports a LD_{50} of 800 mg/kg bw. The available oral acute toxicity data are listed in table 4.1.2.2.*i*, "acute oral toxicity".

Table 4.31 Acute oral toxicity

LD_{50}	Species/sex	Method	Reference
> 2000 mg/kg bw	Rat – male/female	OECD 401, GLP	Sandoz Chemicals (1991)
4000 mg/kg bw	Rat – male/female	OECD 401 (May 1981)	Huels, 1985a
5360 mg/kg bw	Rat – male		Klonne et *al*.,

3620 mg/kg bw	Rat – female		1988/UCC 1985
2990 mg/kg bw	Rat – male		Smyth et *al*., 1969
3500 mg/kg bw	Rat – male/female		BASF, 1971
801 mg/kg bw	Rat – male/female		Shell, 1980
LD0 = 400 mg/kg bw LD100 > 1400 mg/kg bw	Guinea pig (sex not specified)		The Dow Chemical Company, (referred to in OECD-SIDS 2003)

In a rat (Sprague-Dawley) study, performed according to OECD guideline 401 and GLP, five males and five females received 2000 mg/kg bw of ptBP (Sandoz Chemicals, 1991). PtBP was suspended in arachis oil and administered by gavage. No deaths and no signs of systemic toxicity were noted during a 14 days observation period. In the accompanying range-finding study the male died following exposure to 5000 mg/kg bw, whereas the female survived. In the male recieving high dose (5000 mg/kg bw) the following clinical signs of toxicity were reported: hunched posture, lethargy, ptosis, red/brown stains around snout and ataxia. No necropsy was performed. No clinical signs of toxicity were observed in the high-dose female.

In a rat study (Hüls, 1985a), performed according to OECD guideline 401, ptBP was solubilised in paraffin oil and administered by oral gavage. Five male and female Wistar (Bor:WISW) rats were exposed at the lowest dose (3160 mg/kg bw), and 10 males and females were exposed at higher doses (3980 and 5010 mg/kg bw). In the lowest dose group one of 5 males and 2 of 5 females died within 11 days. In the middle dose group 4 of 10 males and 8 of 10 females died within 48 hours. In the highest dose group 7 of 10 males and 5 of 10 females died within 48 hours after exposure. The LD_{50} was calculated to 4000 mg/kg bw. Clinical signs of toxicity included prostration, ataxia, respiratory distress, shivering, hunched posture, bleeding from the nose, diarrhoea and diuresis. Reduced bodyweights were noted in the survivors, but no other signs of toxicity were reported 6 days post exposure. At necropsy the predominant finding was hyperaemia of mucus membranes in the stomach and small intestines, sometimes associated with swelling and with discoloration of liver and pancreas. Hyperaemia of liver, peritoneum and spleen was also noted. Two animals had highly enlarged kidneys.

In a rat (Sprague-Dawley) study (Klonne et *al*., 1988/UCC 1985), groups of five animals (male/female) received ptBP doses of 2500, 3500, 5000 and 10.000 (males only) mg/kg bw. PtBP was given by stomach intubation in a 25% corn oil suspension. No lethality was observed at the lowest dose. Following exposure to 3500 mg/kg bw, 2 of 5 females died. At 5000 mg/kg bw all females died wheraes 2 of 5 males died. At the higest dose all males died. LD_{50} values obtained were 5360 mg/kg bw and 3620 mg/kg bw for male and female rats, respectively. Sluggishness, unsteady gait, prostration, unkempt appearance, and nasal discharge were observed as the principal signs of toxicity. Coloured discharge on fur was reported, in females seen also at the lowest dose levels. The animals were observed for 14 days postexposure. Signs of toxicity subsided in survivors at 3 to 7 days after dosing. All survivors had gained weight at the 7 and 14 post-exposure days. Deaths occurred from 2 hours to 5 days after dosing. In the female rats that died during the study, mottling of the lungs and livers were the principal macroscopic lesions. No significant gross lesions were observed in males.

Groups of 6 male and 6 female Wistar rats were dosed by intubation with 4, 5, 6.3, 7.9 and 10 ml/kg bw of a 10% solution of ptBP in DMSO (equals 400, 500, 630, 790 and 1000 mg/kg

bw) (Shell, 1980). The observation period was 14 days post exposure. The calculated LD_{50} was 801 mg/kg bw. Signs of intoxication were lethargy, bleeding from the nose and piloerection. A clear dose-response relationship was observed. No toxicity reported at the lowest dose (400 mg/kg bw). Three animals (M/F) showed clinical signs of toxicity following 500 and 630 mg/kg bw, whereas all animals at the 790 mg/kg dose showed signs of toxicity and most animals died within hours or days following 1000 mg/kg. Surviving animals generally showed complete recovery within 3-4 days of exposure. Body weight gains were reduced at 7 days, but all survivors gained weight in the 7 to 14 days post-exposure period. Reported mortality was as follows: 400 mg/kg (0/12), 500 mg/kg (1/12), 630 mg/kg (2/12), 790 mg/kg (5/12), 1000 mg/kg (10/12). Only slight differences in the calculated LD_{50} for males and females (786 mg/kg bw and 815 mg/kg bw respectively), but only 2 females survived the highest dose. No data on necropsy was given, and no control group is reported. The volume of the test solution increased (from 3.6 ml/kg to 9.0 ml/kg) with increased doses of ptBP. Thus, in our opinion it is likely that the increasing DMSO-dose influences the toxicity and dose-response relationships observed. This is supported by the difference in LD_{50} in this study compared to the values from adequately performed studies. In the literature LD_{50} values of 17.9 ml/kg bw and 17400-28300 mg/kg bw for DMSO in rats are given. Lethality in mice has been reported at 5 ml/kg bw. For the reasons given above, we believe that the results from the Shell study do not correctly reflect ptBP toxicity and we therefore disregard this study when evaluating the acute oral toxicity of ptBP.

In a list of range-finding toxicity data, an oral LD_{50} of 3.25 ml/kg bw (2990 mg/kg bw - IUCLID) for rats (5 male Carworth-Wistar rats is given (Smyth et *al*., 1969). Substance was administered by gastric intubation. No further information on administration or toxicity is given.

Other routes

After intraperitoneal injection, LD_{50} values of 225 mg/kg (rats) and of 78 mg/kg (ptBP in DMSO, mice) of ptBP have been reported (BASF, 1971; Biagi et *al*., 1975). In the *in vivo* micronucleus test (OECD 474) described in section 4.1.2.7.2 (MHW, Japan, 2003), 5 male and 5 female CD-1 mice were exposed by i.p. injection to 25, 50, 100 and 200 mg/kg bw ptBP in a range-finding experiment. All animals died at 200 mg/kg, and 3 males and 4 females died at 100 mg/kg with severe clinical signs of toxicity. At lower doses (25 and 50 mg/kg bw) in the main study low locomotor acticity was noted. At present, we do not have further details on the toxicity observed. A copy of the complete study protocol, and relevant information will be added to the RAR at a later stage when the whole report has been published.

4.1.2.2.2 Studies in humans

No information regarding a possible lethal dose or signs of acute systemic toxicity in humans was found.

4.1.2.2.3 Summary of acute toxicity

PtBP appears to have low acute toxicity by all three exposure routes. A limit test gives a LC_{50} for inhalation above 5600 mg/m^3 (dust aerosol) with an additional vapour component of 30 mg/m^3. Most studies show dermal and oral LD_{50} values above 2000 mg/kg bw. The exception is an oral rat study (Shell, 1980) that gave a LD_{50} of 801 mg/kg bw. In this study the increasing volumes of DMSO used for intubation of increasing doses of ptBP may be an explanation of the elevated acute toxicity observed in this study compared to the other acute oral toxicity studies reported. The available studies fulfil the Annex VIIA test requirements for evaluation of acute toxicity.

4.1.2.3 Irritation

Several animal studies show that ptBP has irritating properties. In addition, ptBP may induce partial depigmentation of the skin (vitiligo). Depigmentation effects of ptBP is covered in chapter 4.1.2.6.4, "depigmentation".

4.1.2.3.1 Skin

Studies in animals

The irritating properties of ptBP have been addressed in several studies that are summarised in table 4.1.2.2.*ii*, "skin irritation". These studies show effects of ptBP in the range of midly to severely irritating and corrosive to skin.

Table 4.32 Skin irritation

Species	Method	Exposure duration	Result	Reference
Rabbit	OECD 404, GLP	4 hours	Severely irritating	Sandoz Chemicals, 1991
Rabbit (male/female)		4 hours	Non- to moderately irritating. Severely irritating/corrosive to 1/6 animals	Klonne et *al*., 1988/UCC 1985
Rabbit (male/female)	OECD 404	4 hours	Irritating	Huels, 1985b
Rabbit (male/female)	US DOT regulation 173.1300	4 hours	Irritating. Severely irritating/corrosive to 1/6 animals	Schenectady, 1982
Rabbit (male/female)		24 hours	Moderately irritating	Shell, 1980

In an OECD guideline study (OECD 404), following GLP, 500 mg of ptBP was moistened with distilled water and applied (semi-occluded), to the intact skin of three New Zealand rabbits (1 male and 2 females), for 4 hours (Sandoz Chemicals, 1991). Skin reactions were scored according to Draize at one hour, 24, 48 and 72 hours, as well as 7 and 14 days after

dosing. The material produced severe erythema and very slight to moderate oedema. Mean scores erythema: 24 hours, score 4; 72 hours, score 3.4; 14 days, score 0. Mean scores oedema: 24 hours, score 2; 72 hours, score 1.7; 14 days, score 0. Other adverse skin reactions noted were small areas of white-coloured necrosis (all exposed skin sites at 24 and 48 hours), well-defined erythema surrounding scabs, hardened light brown-coloured scab, thickening of the skin, crust formation and reduced re-growth of fur. No irreversible skin alterations were reported after 14d and the substance was jugded to be non-corrosive according to EU classification criteria (full thickness destruction of the skin). The lesions reported indicate that ptBP is irritating to skin.

In another study 3 male and 3 female New Zealand rabbits were dosed with 500 mg ptBP, moistened with water to clipped intact skin under a gauze patch (semi-occluded) for 4 hours (Klonne et *al*., 1988/UCC 1985). Skin reactions were scored according to Draize at one hour, 24, 48 and 72 hours, as well as 7, 10, 14 and 17 days after dosing. No sign of dermal irritation was observed in 4 of 6 rabbits. One female rabbit developed transient erythema (grade 1; day 1) and persisting desquamation (day 10-17), and one male rabbit showed erythema (grade 1-2; day 1-10), minor oedema (grade 1; day 1-3), desquamation (day 10-14), scab formation (day 7-10) and necrosis (day 1-10). This study indicates that ptBP can be irritating and possible also corrosive to skin.

In the percutaneous toxicity study described in chapter 4.1.2.2.1 (Acute toxicity), dermal application of 2000, 8000 and 16000 mg/kg bw ptBP for 24 hours produced severe irritation and dermal necrosis (Klonne et *al*., 1988). Severe skin irritation (including erythema, oedema, fissuring, desquamation and necrosis) were noted in both sexes of all treatment groups. For the middle and high dose groups necrosis generally persisted through the 14-days post-exposure period. For the low dose animals (2000 mg/kg bw) signs of erythema, necrosis and fissuring were present through day 7, whereas desquamation and scabs were present at day 14.

In a study following OECD guideline 404 employing small white Russian, Chbb-SPF, rabbits ptBP was found to be irritating (Huels, 1985b). Five hundred mg ptBP was applied to abraded rabbit skin (3 animals /sex) for a period of 4 hours. Skin reactions were scored according to Draize at one hour, 24, 48 and 72 hours, as well as 6, 8, 10, and 14 days after dosing. Erythema was well defined in 2 of 6 animals and moderate to severe in 4 of 6 animals. Oedema was very slight in 4 of 6 animals, and moderate in 2 of 6 animals at 24 hours. Erythema and oedema was present in some animals through day 10. Scabs and desquamation persisted in 3 of 6 animals at day 14. This study indicates that ptBP is irritating to skin.

In a skin irritation study conducted according to US DOT regulation 173.1300, 500 mg ptBP moistened with salinewas applied for 4 hours (semi-occluded) to the intact skin of New Zealand rabbits (one female/five males) (Schenectady, 1982). Skin reactions were observed after removal of the patch and approximately 48 hours thereafter. Mean scores: Erythema: 4 hours, score 2; 48 hours, score 2.3. Oedema: 4 hours, score 1.5; 48 hours, score 1.7. One male showed necrosis at 48 hours. No further details are provided. The primary irritation index was found to be 3.4 on a scale to 8. This study supports the indications that ptBP can be severely irritating and also corrosive to skin.

Three male and three female New Zealand rabbits were exposed to 500 mg ptBP to intact or to abraded skin for 24 hours in an occlusive patch test (Shell, 1980). Skin reactions were scored according to Draize at 24, 48 and 72 hours, as well as 7 days after dosing. The

following mean scores for non-abraded skin was reported: Erythema: 24h: 1.7; 48h: 1.1; 72h: 0.2; 7d: 0.6.
Oedema: 24h: 0.8; 48h: 0.7; 72h: 0.4; 7d: 0.2. For abraded skin, the mean scores were: Erythema: 24h: 1.8; 48h: 1.7; 72h: 1.3; 7d: 1.0. Oedema: 24h: 0.8; 48h: 0.8; 72h: 0.6; 7d: 0.3. Three of the animals were reported to have small white areas of skin similar in appearance to a burn. No details of reversibility of these effects were reported. In this study ptBP was regarded as moderately irritating to rabbit skin.

Irritation and corrosive effects were mentioned in another skin irritation test using rabbits (BASF, 1971/IUCLID). We have no further information from this study.
In a depigmentation test (Gellin et al., 1970) described in section 4.1.2.6.4 irritation was induced. 0.1 ml solution of ptBP in various solvents was applied daily to the shaved skin of black guinea pigs for up to three weeks. 1 mg and 5 mg of ptBP induced no irritation and moderate irritation respectively. 10 mg of ptBP in acetone induced severe skin irritation (erythema and oedema extending beyond area of application), whereas 10 mg of ptBP both in DMSO and in propylene glycol induced moderate irritation.

Studies in humans

No studies in humans were located.

4.1.2.3.2 Eye

Studies in animals

PtBP has been shown to be highly irritating to eyes.

In rabbit eyes (New Zealand rabbits, 6 animals) approximately 80 mg of finely ground, dry powder produced severe corneal injury, iritis and severe conjunctival irritation (Klonne et *al*., 1988/UCC 1985). The scoring was conducted according to Draize. The following mean scores were reported: Corneal opacity of grade 1 (1 h) to 3.2 (7d), iris lesion grade 1, conjunctival redness of grade 1.8 (1h) to 2.2 (72h), and chemosis of grade 2.3 (1h) to 3.8 (72h). Due to corneal opacity, the scoring of iris lesions after 4h was not possible in many animals and thus reversibility could not be established. The corneal opacity was still significant 21 days after exposure (mean score 2.5; range 0-4). Application of smaller amounts of the material (10 mg) resulted in similar but less severe effects, which persisted in most eyes for the 21-day observation period. This study shows that ptBP is highly irritating to rabbit eyes.

Six New Zealand White rabbits were exposed to 100 mg ptBP (Shell, 1980). Eye injury was scored at 1, 24, 48 and 72 hours, and 7 days post-exposure according to the method of Draize. The following mean scores were obtained: corneal opacity grade 0 (1h) to grade 1.4 (48h-7d), iris lesions grade 0 (1h) to 0.5 (48h-7d), conjunctival redness grade 2 (1h-48h) to 1.2 (7d), chemosis grade 2.2 (24h) to 0.3 (7d). This study indicates that ptBP is irritating to rabbit eyes.

Severe irritation and probably corrosive effects were mentioned in another test (BASF, 1971). However, no details have been reported.

Studies in humans

No studies in humans were located.

4.1.2.3.3 Respiratory tract

Studies in animals

Respiratory toxicity was observed in the rat acute inhalation study described in chapter 4.1.2.2.1, "acute toxicity" (Klonne et *al*., 1988). Mucosal irritation (perinasal, perioral, and periocular encrustation) and respiratory distress (audible respiration, gasping, and a decreased respiration rate) were observed following exposure to ptBP. The animals were exposed in an animal chamber to ptBP in the form of dust aerosol (of 5600 mg/m^3) with an additional vapour component of 30 mg/m^3.

Studies in humans

No studies in humans were located.

4.1.2.3.4 Summary of irritation

Based on the above information we suggest that ptBP is regarded as severely irritating to eyes, skin and the respiratory system with the following classification (Xi, R37/38-41). However, corrosive effects have been reported (see below, chapter 4.1.2.4). From the available data it seems that in most animals (rabbits) moderate to severely skin irritation is observed. We can find no obvious reasons for the apparent differences in skin irritation potential reported in the studies by Sandoz Chemicals and by Klonne et al. Furthermore, two studies report skin corrosivity occurring in a minority of the exposed animals. Only limited information related to the nature of the corrosivity and necrosis reported is available. Prolonged exposure to high doses of ptBP induces persistent necrosis in the skin of all exposed animals. The available studies fulfil the Annex VIIA requirements for irritation.

4.1.2.4 Corrosivity

In the most recent study conducted according to accepted guidelines ptBP was found to be highly irritating to skin. In this study small areas of white-coloured necrosis were induced, but these lesions were not regarded as a corrosive effect according to EU and American classification criteria (full thickness destruction of the skin on at least one animal/ irreversible alteration of the skin). As no further information on the nature of the white coloured necrosis is provided, we have chosen to accept the classification proposal provided in this study. Two studies have reported the occurrence of skin necrosis in a minority of exposed animals following a 4-hour exposure (Klonne et al., 1988/UCC 1985; Schenectady, 1982). After prolonged skin contact (24 hours) in a dermal, acute toxicity study (Klonne 1988/UCC 1985) necrosis was reported in all exposed animals. Such prolonged exposure studies are not used as a basis for classification.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

In a recent Magnusson-Kligman study to assess skin sensitisation ptBP was found to be not sensitising (Hüls, 1998). The study was conducted according to OECD guideline 406 and according to GLP. Young adult males (<500g) of the Dunkin Hartley, Pirbright White Hsd/Poc:DH [SPF] Guinea Pig strain from Harlan Winkelmann GmbH, Borchen, Germany, 10 test and 5 control animals were used. In a preliminary study appropriate test substance concentrations were established by intracutaneous injection. The consentration in the preliminary study were 0, 0.01, 0.05, 0.1, 0.5, 1.00, 5.00 % of ptBP in corn oil. The two highest concentrations induced necrosis 24 hours after injection.

For dermal occlusive application, two patches on each flank were exposed to 5, 10, 25, 50 % (w/w) ptBP in vaseline. The 25 and 50 formulations caused discrete to intense erythema and swelling combined with necrosis and eschar formation after 48 and 72 hours. The exposure concentrations that were used for the induction phase was 0.5 % in corn oil for intracutaneous induction and 10 % in vaseline for the topical induction, whereas 1 % in Vaseline, the highest non-irritating concentration, was used for the challenge treatment. In the main study the skin reactions to the topical induction were evaluated 49 and 72 hours after application. The challenge treatment was carried out with 1 % test compound in vaseline. The treatment caused no skin reactions. The results demonstrated no evidence of skin sensitisation.

Vehicle and positive control animals in the main study after injection with 0.5 % test substance or with vehicle there were moderate and confluent erythema combined with well defined pustulae after one hour and discrete erythema after 24 hours. In the main topical induction study, 49 and 72 hours after application and treatment with Freund's complete adjuvant (FCA) one week before the 10 % test substance, there were intense erythema and swelling and eschar formations partially combined with bloody scratch wounds. Howevere, there were no reactions neither in the test and control animals at 49 and 72 hours after injection with the test formulation and pretreatment with 0.5 % test substance one week before. Neither did they find any skin reactions at 48 nor at 72 hours after challenge treatment with 1 % test substance in the test group, control animals or in the vehicle controls.

Zimerson (1999) performed a modified Magnusson-Kligman study (GPMT) to assess the skin sensitisation potential of ptBP and cross reactivity between ptBP and p-tert-butylcatechol (ptBC). PtBP was found to be not sensitising. The study was conducted according to OECD guideline 406. Young adult females (300-400g) of the Dunkin Hartley guinea pig strain (from J.A.Sahlin, Malmõ, Sweden) were used. A total of 42 animals were used to test for each test substance for sensitisation of ptBP, p-tert-butyl catechol (ptBC), 2,6-dimethylol p-tert-butylphenol (2,6-MPTBP), 2-methylol p-tert-butylphenol (2-MPTBP), tert-butyl-4-hydroxyanisole (BHA) and 3,5-di-tert-butyl-4-hydroxytoluene (BHT); were 36 animals in the sensitisation study (12 in the negative vehicle control group and 24 in the test substance group). The remaining six guinea pigs served as positive controls (using 2- methylol phenol (MP).

Topical irritancy
A 48-hour occluded patch test in four to eight animals for each compound was used. The test substances, either ptBP or ptBC, were applied to each animal on four patches on the flank: two near the back and two near the abdomen. The applied concentrations were for ptBP (6.0/0.4 % w/v/mol x 1^{-1}) and for ptBC (16.7/1.01 % w/v/mol x 1^{-1}) both were solved either in propylene glycol or acetone (see Table 4.1.2.2 iii). The substances were also applied to the neck. Testing was performed one week after pre-treatment of the guinea pigs with Freund's complete adjuvant (FCA) (Pierce, Rockford, IL). All substances gave topical irritancy at these concentrations.

Intradermal Induction
Three injections on 36 animals (see Table 4.1.2.2 iii) at day 0 were given in a row, on each side of the shoulder: I, 0.1 ml of FCA in water 40 % w/v (corresponds to FCA/water 50/50 v/v); II, 0.1 ml of test substance, either ptBP (1.0/0.67 % w/v/mol x 1^{-1}) or ptBC (3.40/0.20 % w/v/mol x 1^{-1}), in propylene glycol/acetone 90/10 % v/v; III, 0.1 ml of a preparation of a mixture of the test substance, either ptBP or ptBC, and FCA in propylene glycol/acetone 90/10 % v/v in which the concentration of FCA was the same as in I and the concentration for the test substance was the same as in II. All animals were treated on a 2 x 4 cm patch area on the shoulder with 200 µl of a preparation consisting of 10 % w/v sodium lauryl sulphate (SLS) in dimethyl acetamide/acetone/ethanol 99.5 % 4/3/3 v/v/v 24 hours before topical sensitisation. Topical sensitisation was performed on the same skin area with 200 µl of a solution of 6.0/0.40 % w/v/mol x 1^{-1} of ptBP, the suspected sensitizer, on a patch of Munktell 1002 filter paper covered with impermeable plastic adhesive tape and secured with adhesive bandage. The dressing was left for 48 hours.

Challenge
Challenge was performed with non-irritant concentrations for all substances.

Challenge I was performed on 36 animals (see Table 4.1.2.2 iii) 2 weeks after the second stage of induction with the suspected sensitizer or a possible cross-reacting substance. A 24-hour occluded patch test with 25 µl of the test solutions either ptBP (2.0/0.13 % w/v/mol x 1^{-1}) or ptBC (7.5/0.45 % w/v/mol x 1^{-1}) was performed on the right flank on each of the two patches near the back. The Al-test (Astra Agency, Södertälje, Sweden) on Durapore was used for patch testing. In each sensitisation study, twelve test animals received the suspected sensitizer on both patches near the back. Six received the suspected sensitizer only on the cranially located patch while vehicle alone was applied to the other patch. Six other animals received the vehicle alone on the cranially located patch and the suspected sensitizer to the other patch.
Six animals received the suspected sensitizer on both patches near the back. Three others received the suspected sensitizer on the cranially located patch and the vehicle alone on the other patch. The same number of animals received the vehicle alone on the cranially located patch and the suspected sensitizer on the other patch. Only one of twenty four animals in the test group was positive to ptBP in challenge I.

Challenge II was performed on 36 animals (see Table 4.1.2.2 iii) at the same time as challenge I but on the left flank. Six patches were tested on 24 test and 12 control animals: two patches near the back, two near the abdomen, and two between the back and abdomen. The animals were challenged with the sensitizer ptBP (2.0/0.13 % w/v/mol x 1^{-1}) or possible cross-reacting substances like ptBC (10.0/0.60 % w/v/mol x 1^{-1}), 2-MPTBP (21.8/1.21 % w/v/mol x 1^{-1}), 2,6-MPTBP (25.4/1.21 % w/v/mol x 1^{-1}), BHA (10.9/0.61 % w/v/mol x 1^{-1}) or BHT

(13.3/0.61 % w/v/mol x 1^{-1}). None of the animals induced with ptBP in the test group was positive to ptBP in challenge II while nine which were induced with ptBC were positive when they were challenged with ptBP.

Controls
The six animals in each control group were treated in the same manner, with regard to the induction and challenge procedure, as the corresponding animals in the test group, except that the suspected sensitizer was not administrated during the induction. Three of six were positive when they were tested with 2-methylol phenol (2-MPTBP). In challenge II four of the animals induced with ptBC were positive to the control substance and three induced with ptBP were positive to 2-MPTBP.

All six animals in the "positive" control group were sensitised and challenged with 2-MP according to procedures described by Bruze (1985).

All animals were evaluated by the minimum criterion of an allergic (positive) reaction: confluent erythema.

Summary of the study:
After induction and challenge with ptBP, only one of 24 (4 %) animals in the test group reacted positively.
In the group of animals subjected to induction with ptBC, nine of 24 (37.5 %) animals reacted positively to ptBP (P=0.014).
This study indicates that ptBP have very low sensitisation capacity, however, exposure to ptBC can lead to cross-reactions with ptBP.

Table 4.33 Induction and challange with ptBP or ptBC and cross-reaction studies between ptBP, ptBC, 2-MPTBP, 2,6-MPTBP, BHA and BHT in Dunkin Hartley guinea pigs.

Procedure (Vehicle)	Number of exposed animals (Test substance/vehicle)	Substance (Concentration in %w/v/molx1^{-1})					
		ptBP	ptBCptBC	2-MPTBP	2,6-MPTBP	BHA	BHT
MP (positive control)	6						
Topical (ac)	4-8	6.0/0.4	16.7/1.01				
Induction ID (pg/FCA/ ac)	24/12	1.0/0.67	3.4/0.20				
Challenge I (pg/ac)	24/12	2.0/0.13	7.5/0.45				
Challenge II (pg/ac)	24/12	2.0/0.13	10.0/0.60	21.8/1.21	25.4/1.21	10.9/0.61	13.3/0.61

ID = intradermal; ac = acetone; pg = propylene glycol; FCA = Freund's complete adjuvant; ptBP = p-tert-butylphenol; ptBC = p-tert-butyl catechol; 2-MPTBP = 2-methylol p-tert-butylphenol; 2,6-MPTBP = 2,6-dimethylol p-tert-butylphenol; BHA = tert-butyl-4-hydroxyanisole; BHT = 3,5-di-tert-butyl-4-hydroxytoluene; MP=2-methylol phenol.

Malten (1967) performed two sensitisation experiments with ptBP-formaldehydresine (ptBP-FR) and free ptBP on white female guinea pigs (no information about the strain). These studies are old and were not conducted according to current guidelines. The results are of limited value in assessing ptBP sensitisation.

In the first study twenty white female guinea pigs were painted on the bare skin behind their ears with one drop of 30 % ptBP-FR in ethyl acetate daily for three weeks followed a two week rest and a second exposure on the left nipple with 1 % ptBP and on the right nipple with 0.5 % ptBP-FR both dissolved in ethyl acetate. Forty-eight hours later nipple biopsies were performed. Ethyl acetate had in previous experiments proven not to be noxious. Histologically 15 of 20 guinea pigs showed contact allergic reactions to the resin and 7 of these 15 animals, in addition, showed positive reactions to ptBP. The results are only described as positive or negative without any further detailed description.
In a second identical study twenty white female guinea pigs were painted with one drop of 30 % ptBP and tested with one 1 % ptBP on the left nipple and with 0.5 % ptBP-FR on the right nipple. Exposure timetable as in experiment I. Fourteen guinea pigs were sensitised with ptBP and 9 of these also reacted to ptBP-FR. There was no information on how this contact allergy was scored.

Respiratory tract

No studies available

4.1.2.5.2 Studies in humans

Skin

Several predictive human studies are available. Most of the human studies are performed with ptBP-formaldehyde resin (ptBP-FR) and not ptBP it self (Fisher *et al*., 1995; Massone *et al*., 1991; Beetz, 1971; Geldof *et al*., 1989; Rycroft *et al*., 1980). These studies, except Geldorf et al., 1989, are not included in this risk assessment.

The reaction to ptBP-FR might be due to the degradation of the product, since the observed effects with ptBP–FR are likely to be caused by degradation products such as 2-hydroxymethyl ptBP and 2,6-dihydroxymethyl ptPB and other unidentified by-products (Malten *et al*., 1985; Rudner, 1977; Hausen *et al*., 1985; Brugnami *et al*., 1982; Budde *et al*., 1988). Only the Rudner, 1977, study is included in the risk assessment of ptBP.

Table 4.34 Detailed descriptions of the human patch tests

Patch test with ptBP	Number of exposed individs	Previous exposure	Present exposure	Vehicle	Test guideline*	Result	Reference
patients allergic to cellulose ester plastics	6	0.5 % ptBP in Celluloics	2 % ptBP	petrolateum	ICDRG	one patient with positive reaction	Jordan, 1972
patients with contact dermatitis	1900 (1974-75 series)	N.I.	3 % ptBP	N.I.	Al-test and Dermicel tape	36.1 (1.9 %) patients with positive reactions	Rudner, 1977
patients with contact dermatitis	900-2000 (1975-76 series)	N.I.	2 % ptBP	N.I.	Al-test and Dermicel tape	Between 10 and 22 patients with positive reactions	Rudner, 1977
patients with severe contact leukoderma	9	ptBP in flakes	1 % ptBP	petrolateum	Standrad Spanish contact dermatitis research group series	all showed positive reactions	Romaguera, 1981
patient with no previous history of skin disease	1	ptBP or ptBP-FR from shoes	2 % ptBP	petrolateum	European standard series and shoe series	positive (++) reaction after 21 days	Chalidapongse, 1992
patients hypersensitive to ptBP-FR	12	ptBP-FR	1.2 % ptBP	water	ICDRG	negative reactions	Zimerson, 2002
Patch test with ptBP-FR and ptBP							
shoemakers with eczema	10	glue with ptBP	50 % ptBP	ethylacetate	7mm^2 Patch test with 12 different substances patients back coverd with cellophane 15mm^2 for 24 h	positive reactions from erythema and edema or papules	Malten, 1958, 1977
shoemakers with eczema	10	glue with ptBP	50 to 75 % ptBP-FR	ethylacetate		to erythema+edema +papules+a few vesicles	Malten, 1958, 1977
shoe manufacturing workers	246 (201 F + 45 M)	glue with ptBP among other things	2 % ptBP and	petrolateum	van der Bend patch test camber, Nederlands using ICDRG criteria	5 reacted allergic contact dermatitis to ptBP-FR but was negative according to ptBP	Mancuso, 1996
patients suspected to have occupational skin disease	359	allergens in glue or plastics	1 % ptBP	petrolateum	ICDRG	3 (0.8 %) patients showed an irritations respons to ptBP	Kanerva, 1999
	308(of 359)		5 % ptBP-FR	petrolateum	ICDRG	8 showed allergic reaction and 5 showed irritation reactions to 5 % ptBP-FR.	
patient exposed to cosmetics	1	ptBP-FR	2 % ptBP	N.I.	True test (Pharmacia)	positive (++)	Angelini, 1993
patients with suspected contact dermatitis	1966	N.I.	1 % ptBP-FR and 1 % ptBP	petrolateum	ICDRG	30 were positive to ptBP-FR and 3 were positive to ptBP in a follow-up study 10 of the 30 were positive for ptBP	Geldof, 1989

* all human test series are performed by different commercial standard series without any further details; N.I. no information available

Patch tests with ptBP

One of six patients allergic to cellulose ester plastics, where ptBP is used as an antioxidant, showed an allergic reaction to a 2 % solution of ptBP in *petrolateum* in a patch test as described in the International Contact Dermatitis Research Group (ICDRG) standard test series (Jordan *et al*., 1972). The concentration of ptBP in cellulosic is 0.5 %.

Patients from the North American Contact Dermatitis group were routinely tested in 1974/75 for skin sensitisation (Rudner, 1977). Of the 1900 patients with contact dermatitis 1.9 % gave positive reactions. An additional study 1975/76 with at least 900 contact dermatitis patients revealed 1.1 % positive reactions to a 2 % concentration of ptBP.

Eight workers from two factories manufacturing ptBP, used as an intermediate in the production of other substances, were patch tested with 1 % ptBP. Patch tests with ptBP were positive in all patients (Romaguera *et al*., 1981).

One patient with a history of skin disease developed heel dermatitis (Chalidapongse *et al*., 1992). She was patch tested with the European standard series and a shoe series, which includes 2 % ptBP in petrolateum, with negative results. However, 21 days later she developed a strong positive reaction at the patch area. She was re-exposed 30 days later on a different patch site. At day 21 post exposure, she developed a positive patch reaction to 2 % ptBP.

General comments to patch testing with ptBP
Most of the human studies with ptBP showed variable positive patch responses. In two of the studies (i.e. Rudner, 1977 and Romaguera et al, 1981) there was clear positive response in a substantial portion of the patients. Furthermore, the positive response observed in these two studies is supported by positive findings in several single case studies. All these studies are performed according to international patch test criteria (se table 4.1.2.2.iv). The patch test used in these studies is the most updated tests available when these studies were performed. The studies all vary in use of solvent, the number of patient tested and previous exposure to different substances probably containing ptBP or ptBP-FR. These patients have a history of skin diseases. The last study is published more recently and is negative. The data seems to be contradictory. However, it is recognized that the studies are mainly performed according to well known international recommended patch test methods and evaluation criteria. The seemingly contradictory results can partly be explained by a modification in the production of ptBP-FR from 1960-1970, see explanation in the summary of sensitisation.

Patch tests with ptBP and ptBP-FR
Twelve patients hypersensitive to ptBP-FR were patch tested according to ICDRG criteria with ptBP, ptBP-FR, formaldehyde and 3 closely related substances (Zimerson *et al*., 2002). Patch test concentrations were 1.2 % w/v ptBP (81mmol/l), 1.0 % w/w ptBP-FR and 1.0 % w/v formaldehyde in water. No simultaneous reactions or cross-reactions were shown to ptBP, formaldehyde, p-tert-butylcatecol, 2(3)-tert-butyl-4-hydroxyanisole (BHA) or 3,5-di-tert-butyl-4-hydroxytoluene (BHT).

Ten shoemakers with eczema due to occupational exposure to ptBP-containing glues were patch-tested for sensitisation in 1957 (Malten *et al*., 1958: 1977). Positive reactions to the ingredients of the glue, ptBP-FR (50 % in ethyl acetate; three patients: 75 % in ethyl acetate) and ptBP (50 % in ethyl acetate) were observed in all patients. After 24 hours, reactions in the ptBP test consisted of erythema, edema or papules, and some patients showed a few vesicles. After 48 hours, all patients showed these symptoms.

PtBP-FR is widely used in neoprene adhesives in the shoe manufacturing industry and causes frequently occupational allergic contact dermatitis (OACD) (Mancuso *et al*., 1996). Twohundredandfirtysix shoemakers were interviewed, examined and patch tested using standard and occupational patch test series recommended by ICDRG. None of the workers reacted to basic components of ptBP (2 %) or formaldehyd, while 5 (2 %) of the shoemakers reacted to ptBP-FR (1 %). This indicates that there is no skin sensitisation potential for ptBP in this study.

Plastics and glues are common causes of occupational dermatoses (Kanerva *et al*., 1999). Threehundredandfiftynine patients with a suspicion of occupational skin disease were patch tested with ptBP (1 %). None showed allergic reactions to the patch test, but 3/359 (0.8 %) showed irritating reactions. Threehundredandeight patients were patch tested for reaction to ptBP-FR (5 %), 2.6 % showed allergic reaction to ptBP-FR while 1.6 % showed irritation reactions.

PtBP-FR is rarely used in cosmetics (Angelini *et al*., 1993). However, one patient exposed to ptBP-FR in a lip liner got a pruriginous dermatitis in the perilabial zone. She was patch tested with ptBP-FR and showed a positive reaction at day 2 and 3 with the TRUE Test™ (Pharmacia). To confirm that it was ptBP that sensitised the patient she was also patch tested with ptBP (2 %). PtBP alone showed a positive allergic reaction at day 2 and 3 and the patient developed depigmentation at the patch site after 7 days.

Several patients with suspected contact allergy were patch tested according to ICDRG guidelines, including ptBP-FR, free ptBP and phenol-formaldehyde resin (Geldof *et al*., 1989). Of the 1966 patients tested, 1.5 % were positive to ptBP-FR, 0.15 % were positive to free ptBP. In a follow-up study with 30 patients positive to ptBP-FR in the first study, 3.33 % were positive to ptBP, and 87 % were positive to ptBP-FR in the secondary study.

Respiratory tract

A chemical industry worker with history of work-related breathlessness, a bronchial provocation test with ptBP elicited a dual asthmatic reaction (Brugnami *et al*., 1982). There was no other information.

In vitro studies

4.1.2.5.3 Summary of sensitisation

Of the three animal studies reported, two is negative and one is positive. The negative studies use the GPMT test and have been performed according to current test guidelines and GLP. The positive study is an older study and the protocol is not well described. No firm conclusions can be drawn based on the animal studies. However, based on the scientific quality of the studies it appears more likely that ptBP does not cause skin sensitisation in animals.

PtBP has been reported to be the first allergen identified in ptBP-FR (Zimerson and Bruze in Kanerva et al.; Handbook of Occupational Dermatology, 2000). There are several sensibilisation studies performed using patch tests of patients with either work related contact allergy or general allergy. Furthermore, many case reports were found in the literature. Many of them used ptBP-FR and are of limited value in evaluating a possible sensitisation potential for ptBP. The results from these studies/reports give a very variable picture of human sensitisation to ptBP. Exposure to other substances like ptBC can lead to cross-reactions with ptBP (Zimerson (1999)). In Contact Dermatitis of Fisher, 1986, (p. 649) it is stated that in the 1950s and 1960s an excess of free p-tert-butylphenol was present in the resin that frequently caused sensitisation to both the resin itself (PTBPF) and PTBP. It was therefore recommended

to eliminate the excess of free ptBP in the resin by Malten. Thus, earlier human exposure was more likely to have higher levels of free ptBP than current exposure, which consists of lower levels of free ptBP and more of the intermediate and degradation products (Fisher, 1986). Accordingly, patients now allergic to ptBP-FR commonly do not react to ptBP and rarely to free formaldehyde (F). Studies performed before changing the production process are expected to reflect allergic reaction to free ptBP and are of more importance when assessing the sensitisation potential of ptBP than studies performed later (Rudner, 1977; Romaguera *et al*., 1981).

The database for assessing skin sensitisation for ptBP has limitations. The animal data are of varying reliability and are not sufficient to draw any conclusions of ptBP as a sensitiser. The human data are also of limited value since most of the studies shows very few positive results and they are mainly performed on patients with former skin allergy or other skin deseases or there is limited information about the exposure substance. A classification proposal of R 43 was discussed in the Technical Committee on Classification and Labelling. It was concluded that the data did not fulfil the classification criteria.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Systemic toxicity - Studies in animals

Inhalation

No available data.

Dermal

No available data.

Oral

The evaluation of repeated dose toxicity is based on a Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test and a 2-generation reproduction study.

The Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test (OECD 422) were conducted according to GLP (MHW, 1996).

In the 14-days dose finding study (MHW, unpublished, referred to in OECD/SIDS report, 2003), doses of 0 (vehicle), 250, 500 and 1000 mg/kg bw/day were administered by oral gavage to Sprague-Dawley rats. Noisy respiratory sound (stridor) and respiratory difficulties, was observed in all dose-groups. Three of 5 females and 1 of 5 males in the highest dose group died up to day 9. At this time, all survivors were dissected but no toxic signs were observed by necropsy. At 500 mg/kg bw/day the only abnormalities reported was noisy respiratory sound in 3 of 5 animals of both sexes. At 250 mg/kg bw/day, 1 of 5 females showed noisy respiratory sound. Respiratory distress was also observed at the highest dose used in the main study described below.

In the main study, 8-week old male and female Sprague-Dawley rats (13 males and 13 females per dose level) were administered ptBP by oral gavage in 0.5 % methyl cellulose at daily doses of 0 (vehicle), 20, 60 and 200 mg/kg bw. The males were administered ptBP for 6 weeks, whereas the females were exposed from 14 days prior to mating to day 4 of lactation.

For the repeated dose toxicity the observations included general condition, food consumption, body weights, haematology, serum biochemistry, gross necropsy, and histopathology of several organs.

Some females of the highest dose group showed stridor, associated with dyspnea (abnormal respiration). The respiratory stress observed was considered to be caused by irritation of the respiratory tract during administration. It is possible that small amounts of ptBP comes in direct contact with the respiratory system during oral gavage and thus induces local irritation. However, histopathological examinations did not reveal signs of irritation of the respiratory tract. The mean plasma concentration of albumin in the males was slightly lower in the 60 and 200 mg/kg dose groups (6 % and 13 %), accompanied by decrease in plasma protein in the 200 mg/kg bw/day males (6 %). A significant lower mean red blood cell count (5 %), and higher mean white blood cell count (38 %) in males in the 200 mg/kg bw/day dose group was also reported. No compound related morphological changes were observed during pathological examination of parental animals. In males there was a slight (less than 5 %) increase in mean relative liver weight. Examination of body weight and gross morphology of the offspring revealed no effects of ptBP. Based on respiratory distress in exposed females and effects on several blood parameters in males, the NOAEL in parental animals from this study is considered to be 60 mg/kg bw/day.

A 2-generation reproduction study in Sprague-Dawley rats with ptBP was performed according to OECD Guideline 416 and US EPA Guideline OPPTS 870.3800 (Clubb and Jardine, 2006). The study is summarized in chapter 4.1.2.9 Toxicity for reproduction. The findings relevant for the evaluation of repeated dose toxicity are described below.

PtBP was given orally in the diet at the following doses 0, 800, 2500 and 7500 ppm, corresponding to approximately 0, 70, 200 and 600 mg/kg bw/day. In the parental generation 28 rats/sex/group were used. The animals were exposed for 10 weeks prior to mating and until termination of lactation.

No treatment related clinical signs were reported. At the two highest doses there was a decrease in body weight gain compared to controls. A statistically significant decrease in body weight gain was reported in males from week 0 to16 of the study at 200 mg/kg bw/day (approximately 90% of control) and at 600 mg/kg bw/day (approximately 70% of control), and in females from week 0 to 10 at 200 mg/kg bw/day (approximately 80% of control) and at 600 mg/kg bw/day (approximately 70% of control). The reduced body weight gain was accompanied by reduced food consumption.

At termination of the experiment in the 600 mg/kg bw/day dose group a statistically significant increase in the weights of the kidneys (4.29 g vs 3.96 g in controls) and liver (20.19 g vs 18.87 g in controls) in males was reported, and in females a statistically significant decrease in the weight of the adrenal gland (0.064 g vs 0.076 g in controls) and ovaries (0.081 g vs 0.107 g in controls) were reported following covariance analysis with the body weight as the covariate. There was a significant increased incidence of minimal to mild vaginal atrophy in high dose females and an increase in the incidence of primordial follicles.

At 200 mg/kg bw/day a statistically significant decrease in the relative weights of ovaries (0.096 g vs 0.107 g in controls) were reported in females as well as reduced relative weights of the adrenal glands that did not reach significans. No significance changes in relative organ weights were reported at 200 mg/kg bw/day in males. At 70 mg/kg bw/day a slight, but significant increase in relative liver weight in males was reported (20.17 g vs 18.87 g in controls). No significant relative organ weight changes were reported for females at the lowest dose.

The NOAEL for repeated dose toxicity is considered to be 70 mg/kg bw/day (800 ppm) from this study based on a dose-dependent reduction of relative weights of ovaries and adrenal glands in females.

Two additional studies address the effects of phenolic compounds, including ptBP, on induction of proliferative lesions of the forestomach and glandular stomach in hamsters and rats (Hirose 1986; 1988). In the first study a group of 7-week old male Syrian Golden hamsters (15 animals) received 1.5 % ptBP in the diet (approximately 1230 mg/kg bw/day, based on an average food consumption of 82 g/kg bw/day, TGD 2003, Appendix VI, Table 3) for a period of 20 weeks. The average body weight was slightly decreased (5 %) compared to the control group. The relative liver weight was increased by approximately 20 %. In the second study a group of 20 Fischer 344 male rats were given 1.5 % ptBP in the diet for 51 weeks. Approximately 8 % decrease in relative liver weight and 13 % increase in relative kidney weight were observed. The dietary exposure of the rats to ptBP can be estimated to approximately 600 mg/kg bw/day (based on an average food consumption of 40 g/kg bw/day TGD 2003, Appendix VI, Table 3). A more detailed description of these studies is given in chapter 4.1.2.8 “Carcinogenicity”.

4.1.2.6.2 Studies in humans

No data avilable.

4.1.2.6.3 Summary of repeated dose toxicity – systemic toxicity

No repeated dose toxicity study according to current Guidelines, OECD 407 (Repeated dose 28-day oral toxicity study in rodent) or OECD 408 (Repeated dose 90-day oral toxicity study in rodent) is available for ptBP. The studies available for evaluation of repeated dose toxicity are an OECD combined repeated dose and reproductive/developmental toxicity screening test (OECD Guideline 422) and a 2-generation reproduction study. The parental NOAEL from the former study was 60 mg/kg bw/day based on respiratory distress in exposed females and effects on several blood parameters in males and 70 mg/kg bw/day in the latter study based on reduced relative weights of ovaries and adrenal glands in females. Long-term exposure to high doses of ptBP in the diet induced forestomach hyperplasia in male rats and hamsters at doses estimated to 600 mg/kg bw/day and 1230 mg/kg bw/day, respectively. In these carcinogenicity studies, moderate effects on relative kidney and liver weights were reported. The respiratory distress reported in the OECD screening study may be caused by the involuntary administration of ptBP into the airways during gavage treatment. This conclusion is supported by the absence of reported respiratory distress in the studies where ptBP was adminestered in the diet. Furthermore, the toxicological significance of the reported alterations in albumin levels and white blood cell counts in males is considered equivocal. For

these reasons the NOAEL derived from the 2-generation reproductive study is considered the most relevant.

A systemic NOAEL of 70 mg/kg bw/day for repeated dose toxicity will be forwarded to the risk characterisation based on effects on relative organ weights reported in the 2-generation reproduction study.

4.1.2.6.4 Skin depigmentation - Studies in animals

There were many studies describing the effect of ptBP on depigmentation of the skin of experimental animals.

0.1 ml solution of ptBP in various solvents was applied daily to an area of 3 x 3 cm^2 to the shaved skin on the back of 12 randomly bred adult male and female, English, short-hair, black guinea pigs (from Mr. Robert Kydd, Chelmsford, Mass., average body weight of 675 g), for up to three weeks (Gellin *et al*., 1970). Five mg and 10 mg of ptBP in acetone induced skin irritation but no depigmentation, while 10 mg of ptBP both in DMSO and in propylene glycol caused strong depigmentation potency.

Several depigmentation tests using male C 57 black mice (5/group) have been conducted. In an oral study administration (3 times a week for 6 months) of 0.2 M of ptBP in 0.2 ml olive oil (6 mg) induced diffuse or patchy depigmentation in the majority of the animals (Hara and Nakajima, 1969). In a second study subcutaneous injection (6 times a week for 7 months) of 0.01 M ptBP in 0.05 ml olive oil (0.075 mg) also induced depigmentation 12 weeks after the first injection (Hara and Uda, 1966; Hara and Nakajima, 1969). Depigmentation of the black hairs was observed and histological findings were studied at the end of the experiment. In the ptBP group, slight changes were evident. In addition, slight changes were observed in the control group injected with olive oil. This was considered to be due to pressure of the papillae by the olive oil, which accumulated, in the subcutaneous tissues. The change in the ptBP-exposed group was fare more marked than in the control group, and the changes in pigmentation were observed on body areas where ptBP was not injected. By the oral administration of ptBP, the pigmentary changes were slight in general, however, definite changes could be seen. A systemic LOAEL for oral administration of ptBP was calculated to be 103 mg/kg bw/day (6 mg x 3days divided with 7 days and divided by 0.025 kg mouse body weight). This LOAEL value will be forwarded to the risk characterisation concerning the risk of depigmentation The lowest subcutaneous injected dose inducing depigmentation in animals is the 0.075 mg ptBP which gives a systemic LOAEL (0.075 mg/day/0.025 kg) = 3 mg/kg bw/day. Since the subcutaneous injection is considered as not relevant for humans this LOAEL value will not be forwarded to risk characterisation.

Vitiligo-like depigmentation in black mice was also observed both by ingestion and by inhalation of ptBP. Cutaneous application in different solvents and at different concentrations did not elicit any skin changes. However, they found distinct depigmentation when using a modified “Kligman solution” (ptBP+ Vitamin A acid + dexamethasone). There was no information on localisation of skin changes or fur changes. Neither was there any information on skin irritation or health observations (Forck *et a l*., 1981).

Daily intramuscular injection of ptBP (7.5 mg/kg and 10 mg/kg) to eight black rabbits induced grey hair on the flanks and backs 12-24 days after the beginning of the injection. By oral administration of 7.5 mg/kg ptBP for 5 days a week for 10 months to 10 wild coloured guinea pigs none of the animals could be considered to show clear cut depigmentation (Malten *et al*., 1971). The lowest dose inducing depigmentation in animals is the 7.5 mg/kg ptBPgives a systemic LOAEL of 7.5 mg/kg. Since the subcutaneous injection is considered as not relevant for humans this LOAEL value will not be forwarded to risk characterisation.

Groups of five adult (average weight 675 g) male and female black guinea pigs were used for testing of various chemicals including ptBP (Gellin *et al*., 1979). Various solvents were used such as DMSO, acetone and hydrophilic ointment. The animals were exposed to 0.1 ml of ptBP at concentration from 0.01 M to 1.0 M for various liquid solvents and from 0.1 % to 10 % for solid ointment bases. The exposure areas (3 x 3 cm^2) on eight dorsal surface sites were shaved weekly. In addition, the unepilated skin of the ears and nipples were used. The test material was applied every weekday for 1-6 months at not specified concentrations. PtBP showed a uniform hypopigmentation with definite but moderate depigmentation potency both at the back and ear but no depigmentation on the nipple. The onset of depigmentation of 0.25 M ptBP in DMSO at the back and ear was 23 days after application and for 10 % in hydrophilic ointment on the back at day 74. The longest time required to induce maximal depigmentation in a single guinea pig was 112 days for 1 M ptBP in acetone on the back. No depigmentation was detected after exposure to DMSO. The histological findings by H & E and silver staining of skin specimens with clinically observed depigmentation was complete absence of melanin in addition to acanthosis and an increase of mononuclear-histocytic cells in the upper- and mid-dermis.

Other studies also indicated that ptBP induced depigmentation of the skin in animals (Zavadskii & Khovanova: 1975). PtBP was applied to the skin of four black guinea pigs for 4 – 5 days and 15 animals were used as control group. Depigmentation occurred without preceding inflammation. Spots of depigmentation (white) were detected on the skin and a zone of hyperpigmentation surrounded the fur-hairs. Leukoderma was irreversible in some cases and exhibited a tendency to progressing and spontaneous dissemination (no further data available).

4.1.2.6.5 Skin depigmentation - Studies in humans

It has been reported that depigmentation was observed in workers handling ptBP in the factory.

In a Russian factory producing ptBP and ptBP-formaldehyde resin (ptBP-FR), depigmentation was observed in 23 of 52 workers (Chumakov *et al*., 1962). The first 3 cases occurred one year after the initial exposure to ptBP/ptBP-FR and in 21 workers the vitiligo had a symmetrical distribution. In Germany, 23 workers handling ptBP (chemical factory, Westfalia) showed depigmentation on the skin of hands and arms after a few months to 2 years of exposure (Forck *et al*., 1981). Some patients exhibited symmetrical depigmentation of body regions covered with clothing that could not caused direct exposure on the skin but more likely by ingestion or inhalation. Several other reports also showed ptBP-induced depigmentation by occupational exposure (Rodermund *et al*., 1975a, Rodermund and Winkler

et al., 1975 (b), Rodermund and Wieland: 1975a, Budde and Stary: 1988, Goldmann and Thiess: 1975, 1976, Ebner *et al*., 1979, Gebhart *et al*., 1980, James *et al*., 1977, Wozniak and Hamm: 1977, Bleehen and Sharquie: 1981).

Based on these studies, ptBP is considered to induce depigmentation of the skin in humans. This effect was likely induced not only via a direct contact with the skin but also via inhalation or ingestion routes.

Nine workers with leukoderma from two different factories (Derfesa and Givaudan) were patch tested for ptBP (Romaguera *et al*., 1981). One of the workers was excluded from the test since he had typical vitiligo from his youth and a family background of this illness. All of the other 8 workers showed positive results after handling ptBP. They showed leukoderma on hands and forearms, sometimes wrists, neck and neckline. The four patients from Derfesa showed an achromic response to the patch test 8 to 15 days later. The workers from Givaudan were positive after 48 and 96 hours.

In an epidemiological study of 246 workers, sensitised by previously exposure to ptBP-FR and free ptBP in glue, in 5 different shoe factories were interviewed, examined and patch tested (2 % ptBP and 1 % ptBP-FR) (Mancuso *et al*., 1996). Two workers of 70 cases (2.8 %) from the assembly part of the factory (prepatation and glueing of shoes) had vitiligo-like leukodermic patches on the backs of their hands and forearms.

Several other patch test studies have been performed with ptBP or ptBP-FR, however, all these were negative concerning depigmentation (James *et al*., 1977; Takeshi *et al*., 1977; Bajaj. *et al*., 1990; 1996). James and coworkers detected vitiligo in 54 of 198 workers exposed to ptBP during manufacture. In this study they report the development of vitiligo by a systemic mechanism due to vapourisation of ptBP in the distillation stage and to dust in the pastillating and packing shed. The dust level varied between 10-100 ppm of ptBP. Twenty of the 54 men were patch tested with 2 % ptBP and all were negative.

Takeshi and co-workers described a worker from a polyestder resin plant who had developed occupational leukoderma after contact with ptBC and also cross-reaction to ptBP. This patient was patch tested with 0.05 % ptBP. He developed positive reactions (no further information on evaluation of this positive reaction) to the patch test but no depigmentation. These data will not be brought further to risk characterisation due to cross reaction from exposure to ptBC and not ptBP.

Bajaj and coworkers (1990) analysed 100 consecutive cases of contact depigmentation due to bindi. Bindi adhesive material was found to contain 80 % ptBP by thin-layer chromography, infrared spectrophotometry and HPLC. Fifteen of the 100 patients were patch tested with bindi adhesive material, 2 % ptBP and 1 % ptBP-FR. 10 normal controls and 14 cases of vitiligo were patch tested with 10 % and 50 % ptBP in plastibase. The patients and controls were observed for a period of 2 months after patch testing. Five of the 15 patients patch tested with the bindi adhesive material showed positive patch test reactions of irritant nature. None of the patents tested with ptBP or ptBP-FR showed positive reactions. Among the 10 normal controls and 14 cases with vitiligo, patch tested with 10 % ptBP five of the controls and 6 of the cases with vitiligo had positive (irritant) reactions. Positive (irritant) reactions were detected in 7 controls and 13 cases with vitiligo after patch testing with 50 % ptBP. In a follow up after 2 months all test sites were normal in both groups.

Bajaj and coworkers (1996) studied 19 cases with footware dermatites were 5 of these had vitiligo. In six other cases there were histories of dermatitis preceding depigmentation. All patients were patch tested with 2 % ptBP in petrolateum and 1 % ptBP-FR in petrolateum. All patients tested negative.

In a study by Mathur and co-workers two cases had depigmentation that was correlated to ptBP since the bindi used could contain 80 % ptBP (Mathur *et al*., 1991). Both females had a history of depigmentation in the location of the adhesive-coated commercial available bindis. Both patients were patch tested with commercial available Bindi, adhesive paste and emplastrin resin. One of the patients developed a 1+ reaction after 2 days to commercial bindi. Both showed 2+ reactions to the adhesive paste after 1 day. No systemic disorders were noticed in either case and both patients had regained normal pigmentation in a follow-up of the study 10 month later.

Depigmentation reactions from substances that are structurally related to ptBP, such as monomethyl ether of hydroquinone (MBH) (used in adhesive material in shoes and Bindi), have been shown in all the above studies.

Electron microscopic investigations of biopsies of depigmentated skin areas from five patients exposed to ptBP revealed a lack of melanocytes in 4 of 5 biopsies (Malten *et al*., 1971). In the biopsy of the 5th patient, melanocytes could be found but with difficulty (these cells shows swollen mitochondria, many vacuoles and only premelanosomes with abacus type pigment distribution instead of solid pigment of mature melanosomes). There were no important deviations in the keratinocytes surrounding these defective melanocytes. In another microscopic evaluation of ten workers exposed to ptBP, the absence or reduction of melanine and melanocytes was observed (Ebner *et al*., 1979; Gebhart *et al*., 1980). Dermal macrophages containing melanine were found. No hyperpigmentation occured in the border zone to normal areas.

A human exposure study by Ikeda et al, 1978 (see human exposure page 27 for details) have shown that industrial exposure for ptBP detected in urine may cause depigmentation at high doses. However, since there are no information about the exposure dose or route this will not be discussed any further in the risk characterisation.

The systemic LOAEL of 103 mg/kg bw/day will be forwarded to the risk characterisation concerning risk of depigmetation.

4.1.2.6.6 Summary of repeated dose toxicity - skin depigmentation

There are several human and animal studies on depigmentation by ptBP, however, most of these studies in humans are concluded on sensitisation reactions and not depigmentation. There are conflicting results in these studies and there is a discussion within the scientific community regarding possible false positives and false negatives in the human studies due to the use of different solvents and lack of proper controls. A systemic $LOAEL_{animal}$ for oral administration of ptBP in C57 black mice was calculated to be 103 mg/kg bw/day [6 mg x 3

days divided with 7 days and divided by 0.025 kg (mouse body weight)]. This systemic $LOAEL_{animal}$ of 103 mg/kg/d will be forwarded to the risk characterization concerning risk of depigmetation.

The lowest subcutaneous injected dose inducing depigmentation in C57 black mice is the 0.075 mg ptBP which gives a systemic $LOAEL_{animal}$ at 3 mg/kg bw/day [0.075 mg/day divided with 0.025 kg (mouse body weight). Since the subcutaneous injection is considered as not relevant for humans this LOAEL value will not be forwarded to risk characterisation.

Overall there seems to be sufficient evidence that ptBP can cause depigmentation in humans and this is supported by animal studies. Animal studies have shown depigmentation after patch tests with 10 mg of ptBP both in DMSO and propylene glycol as solvents. Human studies have shown depigmentation at concentrations of ptBP ≥ 50 %. However, there are some studies in humans showing depigmentation at 2 % ptBP and one study showing reduced production of melanin and lowering of melanocytes in the exposed area. The depigmentation is reversible after some months when the inducing material is removed from the skin. Due to these data an estimated local LOAEL for humans due to the dose in a patch test drop. The volum of a drop is estimated to be in the range of 30-50µl of 2 % solution of ptBP. This gives a local LOAEL for humans in the range of 0.0086 to 0.014 mg/kg [(20g/l ptBP x 0.000030 l x 1000 mg/g /70 kg (weight of a man); (20g/l ptBP x 0.000050 l) x 1000 mg/g /70 kg (weight of a man)]. This is an estimanted local LOAEL based on a patch test drop this will not be discussed in the risk characterisation. A human exposure study by Ikeda et al, 1978 (see human exposure page 27) have shown that industrial exposure for ptBP detected in urine may cause depigmentation at high doses but since there are no information about the exposure dose or route this will not be discussed any further. Another study by Bajaj et al., (1996) showed that some footwear may induce depigmentation related to adhesives used in shoemaking in tropical countries outside EU, however, this is not considered relevant within EU countries.

Depigmentation is not considered an irritative effect and no classification for irritation based on this effect is suggested. However, the systemic LOAEL of 103 mg/kg bw from the study by Hara and Nakajima (1969) will be brought further to the risk characterisation.

4.1.2.6.7 Overall summary of repeated dose toxicity – systemic toxicity

No repeated dose toxicity studies according to current Guidelines, OECD 407 or OECD 408, are available for ptBP. The available study for evaluation of repeated dose toxicity is a 2-generation reproduction study according to OECD Guideline 416 (Clubb and Jardine, 2006). From this study a systemic NOAEL of 70 mg/kg/day for repeated dose toxicity will be forwarded to the risk characterisation. This NOAEL will be used for all scenarios in the risk characterisation except for depigmentation.

Concerning depigmentation, the available human studies is of low quality and the lack of information in the studies renders these studies less suitable to be used in the risk characterisation. However, there is a single dose depigmentation study performed on C57 black mice exposed orally for ptBP which is the basis for a systemic LOAEL of 103 mg/kg/day. This LOAEL will be forwarded to the risk characterisation to scenarios where there is risk for depimentation.

The reason for using two different values for repeated dose toxicity and depigmentation is based on the fact that the systemic NOAEL is from a study with albino Sprague-Dawley rats in the 2-generation study. This strain of rats is not suitable to be used for detection of depigmentation. The only study with reliable data and information showing depigmentation is a single dose oral exposure study on C57 black mice resulting in a the systemic LOAEL of 103 mg/kg/day.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies in vitro

Bacterial tests

In a bacterial reverse mutation assay using S. typhimurium strains TA100, TA1535, TA98, and TA1537 (Ames test) as well as Escherichia coli WP2 uvrA, no gene mutations were induced (SIDS program, 1996). The cytotoxic concentration for bacteria in the presence metabolic activation was 500 µg/plate for all five strains; while without metabolic activation it was 500 µg/plate for TA100, TA1535, TA1537 and 1000 µg/plate for WP2 and TA98. The test was performed according to the guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD guidelines 471 (471/472) and is according to GLP. The amounts of ptBP per plate were; 0, 15.6, 31.3, 62.5, 125, 250 and 500 µg/plate for the TA strains, and 0, 31.3 to 1000 µg/plate for the WP2 strain. The purity of the test substance was 99.9 %. DMSO was used as a solvent in the plate incorporation method. Tests were performed in the presence as well as in the absence of an external metabolic activation system (rat liver S9 mix). Three plates per concentration were used and all tests were performed in duplicate. There was no available information regarding use of positive control in this study.

In another bacterial test no genotoxic effects were observed up to 1000 µg/plate (Dow Project No.: 44/901 unpublished 1992a). The tester strains S. typhimurium TA1535, TA1537, TA98, and TA100 and E. coli WP2 uvrA were treated with the test substance using the plate incorporation method at five dose levels in triplicate, both with and without the addition of a rat liver metabolising system (S9). The amount of ptBP per plate was in the first test 0, 1.6, 8, 40, 200, 1000 µg/plate with appropriate positive test compounds. In the second test 0, 31.25, 62.5, 125, 250, 500, 1000 µg/plate were used. The study was performed according to GLP. DMSO was used as a solvent. The tests were performed in duplicates. Positive controls with metabolic activation: 2-Aminoanthracene at 2 µg/plate for TA 1535 and 10 µg/plate for $WP2_{uvr}A^-$ and Benzo(a)pyrene at 5 µg/plate for TA 100, TA 1537 and TA 98. Positive controls without metabolic activation were: N-ethyl-N'-nitro-N-nitrosoguanidine at 2 µg/plate for $WP2_{uvr}A^-$, 3 µg/plate for TA 100 and 8 µg/plate for TA 1535, 9-Aminoacridine at 80 µg/plate for TA 1537 and 4-Nitoquinoline-1-oxide at 0.2 µg/plate for TA98. Cytotoxicity was observed at 1000 µg/plate. No significant increase in the numbers of revertants was recorded for any of the bacterial strains with any dose either with or without external metabolic activation. PtBP was found to be non-mutagenic under the present test conditions.

PtBP was not genotoxic in S. typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 as well as in E. coli WP2 and WP2 uvrA. The amount of test substance used was 0,

125, 250, 500, 1000, 2000 and 4000 µg/plate in the presence and absence of metabolic activations (Dean et al., 1985). These experiments were performed from 1975 to 1985 and done in triplicate or quadruplicate (until 1980). Several positive controls were used in this study but there is no further information about the doses used and to which bacteria strain they were used. Positive controls were ethyl methanesulphonate (EMS), methyl methanesulphonate (MMS), cyclophosphamide (CP), benzo(a)pyrene (B(a)P), neutral red (NR), sodium azide (SA), 7,12-dimethylbenzanthracene (DMBA), 4-nitroquinoline-N-oxide (NQO). B(a)P, NQO and DMBA was all dissolved in DMSO while the other positive controls were dissolved in aqueous solutions. The purity of the test substance was reported to be > 95 % and DMSO was used as a solvent.

Non-bacterial tests

PtBP was not mutagenic in an *in vitro* mammalian cell gene mutation assay (Dow Project No.: 44/902 unpublished 1992c). L5178 TK +/- mouse lymphoma cells were treated with ptBP at five concentration levels for 3 hours at 37 °C, in duplicate in the presence and absence of S9 mix. The concentration range, selected from the results of a preliminary cytotoxicity test (0, 5, 10, 20, 40, 80 µg/ml) were 0, 5, 10, 20, 40, 60 µg/ml, since at 80 µg/ml cytoxicity was observed. The study was performed with both positive (EMS-S9 mix and CP+S9 mix) and negative (DMSO) controls with and without metabolic activation for 3 hours at 37 °C. The response in the negative controls were just outside the range of 1-10 x 10^{-5} mutants per survivor that is normal for the TK +/- locus in the L5178Y cells but this is likely not to affect the integrity of the test. Both the positive control substances produced marked increases in the mutant frequency per survivor indicating that the test system was operating satisfactorily and that the metabolic activation system was active. The study was conducted according to OECD guideline 476, following GLP. PtBP did not induce increases in mutant frequency at any dose level, either with or without metabolic activation. PtBP was non-mutagenic under the conditions of the study.

PtBP was demonstrated to have no significant mutagenic potential in the mouse lymphoma TK+/- locus assay in L5178Y cells at a concentration of 0, 20, 40, 60 and 80 µg ptBP/ml following 3-6 hour exposure, either with or without metabolic activation (Honma *et al*., 1999). However, ptBP 0, 20, 40, 60 and 80 µg ptBP/ml was shown to be mutagenic following a 24-hour exposure period. However, the mutagenic potential was investigated up to a sufficient cytotoxic condition (<20 % relative survival (RS) as a rule) and at 40µg/ml ptBP the RS was less than 20 % for the 24 hour exposure. Each experiment was performed with a single culture per treatment without S9 mix. The test was not performed according to the OECD TG 476. The actual mutant frequencies obtained following 24-hour exposure was for 30 µg/ml about 100 MF(x 10^{-6}), 40 µg/ml about 150 MF(x 10^{-6}) and 50 µg/ml about 230 MF(x 10^{-6}). The actual concentrations appear to be different than from the reported above. These concentrations are extracted visually from figure 1 (in the paper of Honma *et al*., 1999) and are not consistent with the exposure doses).

Table 4.35 Summary of ptBP on gene mutatation data in vitro

Assay	Strain	Metabolic activation	Cyto toxicity	Dose/concentration of ptBP	Result	Solvent	GLP	Ref.

Assay	Strain	Metabolic activation	Cyto toxicity	Dose/concentration of ptBP	Result	Solvent	GLP	Ref.
Bacterial mutation / Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537 *E. coli* WP2P *uvr*A	+ / - + / -	+S9 500µg/plate for all TA strains - S9 500µg/plate for TA98 +S9 500µg/plate for WP2 strains -S9 1000 µg/plate for WP2	0, 15.6, 31.3, 62.5, 25, 250 and 500 µg/plate for *S. typhimurium* 0, 31.3, 62.5, 125, 250, 500 and 1000 µg/plate for the *E. coli*	Negative Negative	DMSO DMSO	NI	SIDS program, 1996
Bacterial mutation / Ames test	*S. typhimurium* TA98, TA100, TA1535, TA1537; *E. coli* WP2P *uvr*A	+ / - + / -	1000 µg/plate	**first test**: 0, 1.6, 8, 40, 200, 1000 µg/plate **second test**: 0, 31.25, 62.5, 125, 250, 500, 1000 µg/plate	Negative Negative	DMSO	Yes	Dow Project No.: 44/901 unpublished 1992a
Bacterial mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538; *E. coli* WP2, WP2 *uvr*A	+ / - + / -	NI	0, 125, 250, 500, 1000, 2000 and 4000 µg/plate	Negative	DMSO	NI	Dean *et al*., 1985

Assay	Strain	Metabolic activation	Cyto toxicity	Dose/concentration of ptBP	Result	Solvent	GLP	Ref.
Mammalian mutation	Mouse lymphoma L5178Y TK(±)	+ / -	80 µg/ml	Preliminary cytotoxicity test 0, 5, 10, 20, 40, 80 µg/ml Mutagenicity test 0, 5, 10, 20, 40, 60 µg/ml	Negative	NI	Yes	Dow Project No.: 44/902 unpublished 1992c
Mammalian mutation	Mouse lymphoma L5178Y TK(±)	+ / -	40 µg/ml for the 24 h study	Preliminary test 0, 20, 40, 60, 80 µg/ml exposure 3-6 h Secondary test 0, 20, 40, 60, 80 µg/ml exposure 24h	Negative	NI	No	Honma *et al*., 1999

NI = no information

Chromosomal effects
A test of induction by ptBPon structural chromosom aberrations in CHL/IU cells with exogenous metabolic activation according to OECD TG 473 (OECD, SIDS program, 1996). PtBP induced chromosomal aberrations in Chinese hamster lung cells only in the presence of an exogenous metabolic activation system. Polyploidy was reported with and without an exogenous metabolic activation system, but the high incidences of polyploidy were only observed at cytotoxic concentrations.

Solvent: DMSO
Positive control: Mitomycin C without S9 and Cyclophospfamide with S9
Test

- Doses used: –S9 (continuous treatment, 24 or 48 hours); 0, 0.013, 0.025, and 0.05 mg ptBP/ml.
- Doses used: -S9 (short term treatment, 6 hours); 0, 0.02, 0.04, 0.08 mg ptBP/ml.
- Doses used: +S9 (short term treatment, 6 hours); 0, 0.013, 0.025. 0.050 mg ptBP/ml.

Cytotoxicity was detected for continuous treatment at 0.025 mg ptBP/ml and for short-term treatment at 0.08 mg ptBP/ml both without metabolic activation. There was no observation of cytotoxicity with metabolic activation.

Lowest concentration producing cytogenetic effects was: (1) without S9 (continuous treatment) using 0.025 mg/ml (polyploidy), (2) without S9 (short-term treatment) 0.02 mg/ml (polyploidy), (3) with S9 (short-term treatment) 0.013 mg/ml (clastogenicity) and 0.025 mg/ml (polyploidy). After 24 hours the percent polyploidy was 7.63 and after 48 hours 93.18.

Further evaluation of the study was not possible since only an English summary was available, the full study report being in Japanese. The study was conducted according to OECD Guideline 473, following GLP. The purity of the test substance was reported to be 99.9 %. Cytotoxicity was observed at 0.025 mg ptBP/ml (without metabolic activation, continuous treatment) and 0.08 mg ptBP/ml (without metabolic activation, short-term treatment).

In another chromosomal aberration study according to OECD 473 the clastogenic effects of ptBP was assessed in rat lymphocytes (Dow Project No.: 44/903 unpublished 1992b). PtBP is not an inducer of chromosomal aberrations in any of the treatment groups and therefore non-clastogenic under the conditions of the study. Cells were treated with the test material at three concentrations in duplicate with DMSO as vehicle. In an initial experiment 0, 15.63, 31.25, 62.5, 125, 250, and 500 µg ptBP/ml were used. Partial or complete haemolysis was observed at 125, 250 and 500 µg/ml and insufficient or no metaphases were available for evaluation on at least four of the six concentration levels. In the first experiment two treatment conditions were used, i. e. 20 hour continuous exposure in the absence of metabolic activation or 4 hours exposure in the presence of metabolic activation, followed by a 16 or 26 hour expression period. The concentration range was 0, 15.63, 31.25 and 62.5 µg/ml. In the 2nd experiment both 20 hour and 30 hour post-treatment cell harvests were performed.

Positive control:
- 500 µg/ml EMS in the absence of metabolic enzyms.
- 4.2 µg/ml Cyclophosphamide (CP) where S9 was included.

- Experiment I, 20h at 37 °C, concentrations 0, 15.63, 31.25, 62.5 and 125 µg ptBP/ml with appropriate positive test compounds (EMS and CP4.2) ± S9 mix; at 30 h the cells were exposed to 1.9, 3.75, 7.5, 15, 30 and 60 µg ptBP/ml with appropriate positive test compounds (CP4.2) + S9 mix. Sufficient scorable metaphases were available at all of the dose levels used except 125 µg ptBP/ml.PtBP did not induce chromosomal aberration in any of the treatment groups..

- Experiment II, 20 and 30h at 37 °C, concentrations 0, 1.0, 1.95, 3.9, 7.8, 15.63, 31.25, 62.5 and 125 µg ptBP/ml with appropriate positive test compounds (EMS) without S9 mix. The four dose leves between 3.9 and 31.25 µg ptBP/ml were evaluated for chormosome aberrations. The 20 and 30h at 37 °C, concentrations 0,1.88, 3.75, 75, 15.0, 30 and 60 µg ptBP/ml with appropriate positive test compounds (CP4.2) with S9 mix. The four dose leves between 3.75 and 30 µg ptBP/ml for the 20 h cultures and 7.5 µg ptBP/ml for the 30h cultures were evaluated for chromosome aberrations. PtBP did not induce chromosomal aberration in any of the treatment groups.

The study was conducted according to OECD guideline 473, following GLP. PtBP produced no significant increases in the frequency of aberrations in any of the treatment groups and therefore was shown to be non-clastogenic under the conditions of the study.

In another study on mitotic gene conversion in Saccharomyces cerevisiae JD1 and structural chromosomal damage in a cultured rat-liver cell line by ptBP did not induce chromosomal aberrations in rat liver epithelial-type cells (Dean *et al*., 1985). Neither did ptBP induce mitotic recombination in *Saccaromyces cerevisiae* JD1 with or without an exogenous metabolic activation system when exposed for 18h at 30 °C. One stationary and one log-phase conversion assay were performed with 5 % solution of the test substance. The test was performed according to EEC Annex V B16 (Commission Directive 84/449/EEC), following GLP.

PtBP induced chromosomal aberrations and polyploidy in Chinese hamster lung (CHL/IU) cells. CHL/IU cells were treated with 100 to 1000 mM (from the paper the range was from 50mg/ml to 500mg/ml) ptBP dissolved in aceton or DMSO (Kusakabe *et al*., 2002). However, the experimental concentration and solvent used is not clearly described in the publication. Therefore the concentration might be 100 mM (15mg/ml) or 50 mg/ml in water. In order to examine a possible role of metabolic activation of ptBP, the proliferating cells were treated with ptBP for 6 hours in serum-free medium with or without S9 mix, then cultured a further 18 hours in fresh medium with serum. The cells were also treated with ptBP for 24 hours and 48 hours continuously in the absence of S9 mix. Duplicate cultures were used for each experiment. The study was conducted according to OECD TG 473. PtBP induced structural chromosomal aberrations (within the range of <20 % to =>20 %) with the minimum effective dose manifesting severe cytotoxicity (50 % or less) in a short-term treatment assay with S9 mix, and 93.2 % polyploidy in a 48 hour continuous treatment test.

Table 4.36 Summary of in vitro chromosomal aberrations caused by ptBP

Assay	Strain	Metabolic activation	Positive control	Dose/concentration of ptBP	Cyto toxicity	Result	Solvent	GLP	Ref.
Chromo-somal aberration, OECD TG 473	*CHL/UI cells*	+ / -	Mitomycine C –S9 and Cyclophosphamide +S9	-S9 (continous treatment)0, 0.013, 0.025 and 0.05 mg ptBP/ml (short term treatment) 0, 0.02, 0.04 and 0.08 mg ptBP/ml +S9 (short term treatment) 0, 0.013, 0.025 and 0.050 mg	-S9 0.025 mg ptBP/ml at continous treatment and at 0.08 mg ptBP/ml for short-term treatment +S9 No detection of cytotoxicity	positive	DMSO DMSO	Yes	OECD, SIDS program, 1996

Assay	Strain	Metabolic activation	Positive control	Dose/concentration of ptBP	Cyto toxicity	Result	Solvent	GLP	Ref.
				ptBP/ml					
Chromo-somal aberration, OECD TG 473	*Rat lymphocytes*	+ / -	EMS –S9 and Cyclophosphamide +S9	Experiment I 0, 15.63, 31.25, and 65.5 µg ptBP/ml Experiment II 0, 3.9, 7.8, 15.63 and 31.25 µg ptBP/ml	Experiment I Partial or complete haemolysis observed at 125, 250 and 500 µg ptBP/ml. Not possible to evaluate metaphases.	Negative	DMSO	Yes	Dow Project No.: 44/903 unpublished 1992b
Mitotic gene conversion	*Saccharomyces cerevisiae JD1.*	?	NI	NI	NI	Negative	NI	NI	Dean *et al*., 1985
Structural chromosomal damage	*Rat liver cell-line*	?	NI	NI	NI	Negative	NI	NI	
Mitotic recombinarion Annex V B16	*Saccharomyces cerevisiae JD1.*	+ / -	NI	5% solution of ptBP	NI	Negative	NI	Yes	
Chromo-somal aberration, OECD TG 473	*CHL/UI cells*	+ / -	NI	100-1000 µM (15 or 50-500 mg ptBP/ml)	yes	positive	DMSO or water	No	Kusakabe et al 2002

4.1.2.7.2 Studies in vivo

To elucidate *in vivo* genotoxicity of ptBP, a mammalian erythrocyte micronucleus test (i.p. injection) according to OECD Test Guideline 474 was conducted. (MHLW, Japan 2005). PtBP was considered not genotoxic *in vivo.* PtBP was dissolved in 0.5 % methyl cellulose. In a preliminary range-finding experiment 5 males and 5 females were exposed to 25, 50, 100 and 200 mg/kg ptBP. All animals died at 200 mg/kg, and 3 males and 4 females died at 100 mg/kg with severe clinical signs. Based on this preliminary study maximal tolerable dose (MTD) was considered to be 50 mg/kg. A single i.p. injection of ptBP at 0, 12.5, 25 and 50 mg/kg was given to male CD-1 mice age 9 weeks (5 animals in the group, 5 treated animals

per dose), based on severe toxicity at 100mg/kg and no sex difference on toxicity in the previous range-finding study. Two thousand polychromatic erythrocytes (PCEs) of bone marrow cells were counted at 24 and 48 hours after the injection ptBP and compared to the results from the positive control, Cyclophosphamide (CPA) and the negative control methyl cellulose (MC). No significant differences in signs of toxicity between negative control and ptBP-exposed animals were found. The ptBP-exposed male mice showed low locomotor activity at 25 and 50 mg/kg. No increase in the frequency of micronucleated bone marrow cells was observed in any dose groups at 24 and 48 hours after administration compared to control animals.Although the data in this study was not statistically significant, the data indicate that there is a trend to decreased PCE/NCE ratios with dose. In addition, the route of administration in combination with the tested dose (close to MTD) suggests that it is very likely that the material has reached the target organ. Based on these results (see table 1 from the Hara study, reported in MHLW, Japan 2005) ptBP was considered not genotoxic *in vivo*.

In addititon, when they tested the same specimens for chromosomal aberrations there were no detection of chromosomal aberration or spindle body formation in the mouse marrow cells induced by ptBP. PtBP was considered not genotoxic *in vivo.*

Table 1 Results of micronucleus test in male CD-1(ICR) mice after single intraperitoneal injection of *p-tert*-butylphenol

Compound	Dose (mg/kg)	No. of doses	Sampling time(hr)	No. of mice	PCE/ERY a)			No. of PCE observed	No. of MNPCE		MNPCE/PCE	
					% ± SD	(Min/Max)					% ± SD	(Min
p-tert-Butylphenol	0	1	24	5	51.7 ± 3.9	(48.2/57.0)	—	10000	16	—	0.16 ± 0.08	(0.05
	12.5	1	24	5	50.1 ± 6.2	(45.5/57.9)	N.S.	10000	6	N.S.	0.06 ± 0.04	(0.00
	25	1	24	5	54.8 ± 5.7	(47.4/60.7)	N.S.	10000	12	N.S.	0.12 ± 0.06	(0.05
	50	1	24	5	44.3 ± 10.5	(26.0/53.0)	N.S.	10000	9	N.S.	0.09 ± 0.07	(0.00
Cyclophosphamide	50	1	24	5	46.6 ± 9.8	(32.4/51.4)	N.S.	10000	195	***	1.95 ± 0.52	(1.25
p-tert-Butylphenol	0	1	48	5	55.5 ± 4.2	(51.7/61.7)	—	10000	16	—	0.16 ± 0.07	(0.10
	12.5	1	48	5	55.3 ± 6.1	(48.6/62.7)	N.S.	10000	8	N.S.	0.08 ± 0.06	(0.00
	25	1	48	5	50.2 ± 3.6	(45.2/54.2)	N.S.	10000	11	N.S.	0.11 ± 0.04	(0.05
	50	1	48	5	49.6 ± 10.8	(34.3/63.1)	N.S.	10000	6	N.S.	0.06 ± 0.02	(0.05

a) Number of polychromatic erythrocytes/number of erythrocytes observed
b) Number of micronucleated polychromatic erythrocytes/number of polychromatic erythrocytes observed
N.S.: No significant difference from 0 mg/kg, $p \geqq 0.05$
***: Significant difference from 0 mg/kg, $p < 0.001$

An *in vivo* mice micronucleus assay is available for a structural isomer of ptBP, i. e. o-tert-butylphenol (Condea, 2000). The study was conducted according to OECD guidelines 474 and according to GLP. Male and female Swiss-CD mice (5/sex) were dosed once with 250, 500, or 1000 mg/kg via oral gavage. Negative and positive control animals received either the solvent (corn oil) alone, or mitomycin C. Preparation of bone marrow cells was done after 24h. An additional group of animals (5/sex) received one single dose of 1000 mg/kg and bone marrow cells were prepared after 48 hours. Substance related toxic effects were observed in all groups. No increase in micronuclei was observed in any of the test groups. *O*-tert-Butylphenol was not clastogenic under the conditions of the test.

Furthermore, additional data from other alkylphenols (e. g. p-tert-octylphenol, p-nonylphenol) all show that alkylphenols are not mutagenic. In accordance with these findings ptBP is considered non-genotoxic. In the study with o-tert-butylphenol changes were seen in the PCE/NCE ratio indicating that the target organ was reached (CEPAD EBPP, October 31. 2006). And in the study with nonyl-phenol, the PCE/NCE ratio was not affected, but the study was conducted at the maximum tolerated dose and using the intraperitoneal route of administration, therefore, it can be presumed that the exposure of the target organ has occurred (CEPAD EBPP, October 31, 2006). These additional data may also indicate that ptBP which also used a nearly maximal tolerable dose most probably did reach the target organ and therefore is not considered to be a mutagen.

Table 4.37 Summary of in vivo Micronucleus test on ptBP

Assay	Strain	Metabolic activation	Positive control	Dose/concentration of ptBP	Cyto toxicity	Result	Solvent	GLP	Ref.
Micronucleus test, OECD TG 474	*Bone marrow Erythrocyte on CD-1 mice*		No information of positive control	Preliminary range finding study 0, 25, 50, 100 and 200 mg ptBP/kg bw.	Based on this preliminary study maxiumum tolarable dose (MTD) was defined at 50 mg ptBP/kg bw.	Negative	Methyl cellu-lose	Yes	MHLW, Japan in progress, 2003
			No information of negative control	Experiment: 0, 12.5, 25 and 50 mg ptBP/kg.			Methyl cellu-lose	Yes	

4.1.2.7.3 Summary of mutagenicity

P-tert-butylphenol (ptBP) was negative in three bacterial tests. The mouse lymphoma TK+/- locus assays have given both negative and positive results, apparently depending upon duration of exposure. One study performed according to OECD TG 476 and GLP was negative. Another study was also negative after 3-6 h exposure while ptBP appeared to be mutagenic after 24 h exposure.
PtBP induced chromosomal aberrations with an exogenous metabolic activation and polyploidy with and without an exogenous metabolic activation in two studies with Chinese hamster lung cells but not in a study with rat lymphocytes.
Thus, the overall results regarding mammalian cell mutagenicity *in vitro* is inconclusive.

To elucidate *in vivo* genotoxicity of ptBP, a mammalian erythrocyte micronucleus test was conducted. No increase in the frequency of micronucleated bone marrow cells was observed in any dose group.
Although not statistically significant, the data indicate that there is a trend to decreased PCE/NCE ratios with dose. In addition, the route of administration in combination with the tested dose (close to MTD) suggests that it is very likely that the material has reached the target organ.

Based on data from the other alkylphenols and the mutagenicity data on ptBP available, it is assumed that ptBP most likely is not mutagenic.

Based on the available data ptBP does not fulfil the EU criteria for classification as mutagenic.

4.1.2.8 Carcinogenicity

The database for assessing carcinogenicity is limited.

4.1.2.8.1 Studies in animals

Inhalation

No studies available

Dermal

No studies available

Oral

No studies using standard and current test guidelines are available.

Rat

The promoting effect of ptBP and four other phenolic antioxidants on MNNG (N-methyl-N'-nitro-N-nitrosoguanidine) -initiated forestomach and glandular stomach carcinogenesis were investigated in male F344 rats (Hirose *et al*., 1988). Groups of 20 rats (5 weeks old) were given an intragastric dose of 150 mg/kg bw MNNG and starting from one week later the animals received basal diet (Oritental MF basal powdered diet, Oritental Yeast Co. Tokyo, Japan) containing 1.5 % ptBP (purity > 95%) (estimated to be 600 mg ptBP/kg bw, TGD 2003 appendix VI table 3), or basal diet alone for 51 weeks. Control groups receiving basal diet or diet containing ptBP without prior MNNG-treatment, was included.

The final body weights of animals given MNNG followed by ptBP or ptBP without pretreatment with MNNG were significantly lower then those treated with MNNG and basal diet alone. However, liver and kidney weights expressed as g/100 g body weight of animals treated with the chemicals were significantly higher than those of corresponding control groups.

Table 4.38 Histological changes in the f forestomach

Treatment	No. of rats	No. of rats (%)			
		Hyperplasia	Papilloma	Carcinoma *in situ*	Squamous cell carcinoma
MNNG → ptBP	20	20 (100%)	19 (95%)	8 (40%)	15 (75%)[a]
MNNG→ basal diet	19	19 (100%)	13 (68%)	11 (58%)	5 (26%)
PtBP	15	14 (93%)[b]	1 (7%)	0	0
Basal diet	10	0	0	0	0

Significant different from control group at ([a]) $P < 0.05$, ([b]) $P < 0.001$.

PtBP induced forestomach squamous cell carcinoma after initiation with MNNG in F344 male rats (Table 4.40). In addition, one rat had developed an adenocarcinom (5%; not significant) in the fundic region of the glandular stomach.

The induction of forestomach hyperplasia by ptBP in uninitiated rats is probably caused by its irritating effects.

Hamster

The effects of 13 phenolic compounds to induce of proliferative lesions of the forestomach of male Syrian golden hamsters were studied (Hirose *et al*., 1986). Groups of 15 hamsters (6 weeks old) were given 1.5% ptBP (purity > 95%) (estimated to be 1230 mg ptBP/kg bw, TGD 2003 appendix VI table 3) in Oritental MF basal powdered diet for 20 weeks. A control group received basal diet for 20 weeks.

At the end of the experiment, the average body weight of the group receiving ptBP was 5% less than the control group. The relative liver weight was slightly increased (not statistical significant) in the ptBP treated hamsters.

Thickening of the forestomach epithelium with a keratin-like white substance was observed in hamsters treated with ptBP. Histologically, hyperplasia of the forestomach was classified into three different types, mild (< 0.1 mm), moderate (0.1 – 0.5 mm), and severe (> 0.5 mm) depending on the thickness of the epithelium. Another category of change was papillomatous lesions, in which the epithelium showed upward projection with slight atypia of cells, or nestic downward growth beyond the muscularis mucosa.

Table 4.39 Histological changes in the forestomach

Treatment	No. of hamsters	No. of hamsters (%)			
		Mild hyperplasia	Moderate hyperplasia	Severe hyperplasia	Papillomatous lesions
PtBP	15	15 (100%)[a]	12 (80%)[a]	11 (73%)[a]	7 (47%)
Basal diet	15	7 (47%)	1 (7%)	0	0

[a]Significant different from control group at $P < 0.001$.

PtBP induced hyperplasia as well as papillomaous lesions (Table 4.39). In an autoradiographic study, the labeling index in the forestomach increased (P < 00.1) in hamsters treated with ptBP compared with control hamsters.

4.1.2.8.2 Studies in humans

Aschengrau et *al*., 1998 conducted a population-based case-control study to describe the relationship between occupational exposures to estrogenic chemicals and the occurrence of breast cancer in Massachusetts, USA. The study involved 261 cases of breast cancer diagnosed from 1983 through 1986 and 753 controls. 7 cases and 40 controls had any exposure to ptBP (adjusted odds ratio 0.5; 95% confidence interval 0.2-1.2) and 2 cases and 1 control had only exposure to ptBP (odd ratio was not calculated, as there were less than three exposed cases or controls). No conclusions can be drawn from the study due to the low numbers and complex exposures.

4.1.2.8.3 Summary of carcinogenicity

The studies of Hirose and coworkers (1986, 1988) demonstrated that ptBP could induce hyperplasia in the forestomach of rats and hamsters. Papillomatous lesions were also induced in the forestomach of hamsters. In addition, ptBP induced forestomach tumours in an initiation – promotion study in rats after initiation with MNNG. Due to the short duration of the studies (rats less than 1 year; hamsters less than ½ year), it is not possible to draw any absolute conclusions in relation to the possible carcinogenic potential of ptBP alone. Most probably the mechanism of ptBP induction of forestomach tumours is the promoter effect. Moreover, induction of forestomach tumours in rodents by agents without demonstrable genotoxicity may be of little relevance to humans (IARC, 2003).

“For distinction between category 3 and no classification for carcinogen effects arguments are relevant which exclude a concern for man: a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man.” In this case both the place where the tumours are formed (in the forestomach) and that the mechanism is most probably as a promoter are arguments against classification as a carcinogen.

The available studies on carcinogenicity are not sufficient to assess to carcinogenic potential of ptBP, but as ptBP is most likely not mutagenic, it is unlikely that the substance is carcinogenic.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Endocrine modulation

An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism or its progeny through alterations in the function of the endocrine system. *In vitro* assays may be useful in setting priorities for further testing and for supplying information for understanding the mode of action. However, utilising *in vitro* assays for predicting *in vivo* endocrine disrupter effects may generate false-negative as well as false-positive results. Thus, major emphasis should be put on *in vivo* assays. The two-generation study (OECD TG 416) is currently the most complete study available for endocrine disrupters.

Certain alkylphenols are discussed to act as endocrine modulators. In this respect longer chain alkylphenols, i.e. p-nonylphenol and p-tert-octylphenol have the highest activity in several *in vitro*- as well as *in vivo*-assays.

In vitro studies

The following *in vitro* studies are available with regard to endocrine activity of ptBP in screening assays.

The E-screen was used to assess the estrogenicity of ptBP and other environmental chemicals, using the proliferative effect of estrogens/xenoestrogens on their target cells (MCF-7 cells) as an end point (Soto et *al*., 1992; 1995; 1998). Cells were exposed for 6 days, to 10 μM ptBP, other environmental chemicals, and E_2 (concentrations not given). Relative proliferative potencies (RPP, %) were determined, which measures: (the ratio between the minimal concentration of E_2 needed for maximal cell yield and the minimal dose of ptBP needed to achieve a similar effect) x 100. E_2 induced maximal cell yields (Relative proliferative effect, RPE) at 30 pM, whereas ptBP was needed at a concentration of 10 μM for a cell yield at 71%. A RPE value of 100 indicates that the compound tested is a fully agonist; a value of 0 indicates that the compound lacks estrogenicity at the dose level tested, and intermediate values suggest that the compound is a partial agonist. RPP for ptBP was 0.0003% as compared to 100% for E_2. For 4-nonylphenol the lowest concentration needed for maximal cell yield (100 %) was 10.0 μM, with a RPP at 0.001% (Soto et *al*., 1992; 1998). . For 5-octylphenol the lowest concentration needed for maximal cell yield (RPE 100%) was 100 nM, with a RPP at 0.03% (Soto et *al*., 1995). In the discussion it was described that only the p-isomers of alkylphenols were estrogenic. (Soto et *al*., 1991).

In another study the E-screen was used to assess the estrogenicity of ptBP, 17β-estradiol (E2), and other environmental chemicals (Körner et *al*., 1998). The test was based on the induction of proliferation in human estrogen receptor-positive MCF-7 breast cancer cells after 6 days in culture. PtBP at a concentration of 10 μM was tested in four independent experiments each carried out in quadruplicate. The concentration of ptBP which induced maximal cell proliferation (78%) was $1x10^{-5}$ M, compared to a maximal cell proliferation (100%) for E2 at $1x10^{-10}$ M. In comparison, for 4-nonylphenol the lowest concentration needed for maximal cell yield (104%) was $1x10^{-6}$ M.

The estrogen-like activity of ptBP was studied using the estrogen-dependent human breast cancer cell line MCF-7 (Olsen et *al*., 2002). The concentration of ptBP tested was from 10^{-11} to 10^{-5} M. For antagonistic properties the concentrations were 10 or 30 μM. In this study ptBP was shown to bind to the estrogen receptor with approximately 10 000-fold less affinity than 17β-estradiol (the binding affinity was 0.01-0.03% compared to 100% for 17β-estradiol). In this study ptBP also stimulated cell growth. The highest stimulation of cell growth (7 %) was observed at 10 μM of ptBP, compared a lowest concentration of 30 pM for 17β-estradiol inducing a 100% cell growth. PtBP also induced estrogen-regulated proteins such as the progesterone receptor (PgR) and the estrogen-regulated secretorial protein (pS2). A marked elevation (14-fold) of PgR was reported for ptBP at 10 μM and for 17β-estradiol at 30 pM compared to the control. The other phenolic compound tested [4-bromophenol (4-BP), 2,4-dibromophenol (2,4-DBP), 2,4,6-tribromophenol (2,4,6-TP)], gave no induction of PgR at 30 μM compared to the control. As regard pS2, a maximal level of pS2 induced by 17β-estradiol (100%) ranged from 3.8 to 10.53 μg/mg cytosolic protein at a concentration of 30 pM E2, whereas the control varied between 0.8 to 3.59 μg/mg cytosolic protein. Exposure of MCF-7 cells to 17β-estradiol gave a 3- to 11-fold increase of pS2 in the medium. 10 μM ptBP gave a relative induction of pS2 of 39% compared to controls, whereas 4-BP, 2,4-DBP, and 2,4,6-TBP had no influence on the level of pS2. In this study ptBP showed affinity to the estrogen receptor, induced growth of MCF-7 cells, and induced estrogen-regulated proteins such as the PgR and pS2. The brominated phenols, however, although binding to the ER, did not stimulate cell growth or increase the levels of PgR or pS2.

PtBP was shown to bind weakly to estrogen receptor (ER) ERα and ERβ (Kuiper et *al*., 1998). In this study the estrogenic activity of ptBP and other chemicals was studied in a competition binding assays with ERα and ERβ. Serial dilutions of the compounds were tested. PtBP was shown to compete with 17β-estradiol (E2) for binding to both ER subtypes with a similar preference and degree, opposite to what Jobling et al., 1995 found for ERα. In the Jobling et al., 1995 study no information regarding the concentration of ptBP studied was given, the results were only mentioned, however, the concentration of E2 was 10 nM. The relative binding affinity (RBA) for ptBP was < 0.01 for ERα and ERβ, compared to a RBA for E2 at 100 for ERα and ERβ. By comparison the RBA for Bisphenol A was the same as for ptBP, however, for nonylphenol the RBA was 0.05 for ERα and 0.09 for ERβ. The binding affinity was shown to increase with the number of C-atoms in the alkylgroup.

In a study by Routledge and Sumpter, 1997 an estrogen-inducible strain of yeast, *Saccharomyces cerevisia*, expressing the human estrogen receptor was used. The method is called "The recombinant Yeast screen assay". The incubation time was 7 days. E2 concentrations were from 10 nM to 5 pM. PtBP concentrations were from 5 mM to 5 pM. In this study ptBP was shown to be a weak estrogen. PtBP was approximately 1,500,000 times less potent than 17β-estradiol to bind to the human ER receptor. In comparison 4-nonylphenol was 30,000 fold less potent than 17β-estradiol.

The purpose of the study by Aschhengrau et *al*., 1998 was to determine the prevalence of occupational exposure to xenoestrogens as identified by the E-screen bioassay (where ptBP was included), and to describe the relationship between occupational exposure to xenoestrogens and the occurrence of breast cancer, while controlling for established risk factors. In this study exposure to ptBP was not associated with an increase in the occurrence of breast cancer, however cautions in the interpretation of the study has to be taken since it

was based on a small number of exposed subjects, with a limitations in the exposure assessment.

In a study by Van den Berg et *al*., 1991 ptBP was analysed for direct interference with the Thyroxine (T4) binding site of transthyretin (a carrier for both vitamin A and thyroid hormones) using a competitive binding assay. At 100 μM (the only concentration tested) a competition less than 10% was reported, and ptBP was considered to be a very weak competitor. This assay is a sensitive assay owing to the high specific radioactivity of T4, since a 50% competition level (IC_{50}) could be attained by $4x10^{-8}$ M cold T4 under standard assay conditions.

Summary endocrine modulation

These studies indicate that ptBP has the potential to induce proliferation of the estrogen-dependent human breast cancer cell line MCF-7, binding to the oestrogen receptor, and induce oestrogen-regulated proteins, however, with an affinity 10 000-fold less than 17β-estradiol. PtBP was shown to be 10 000 to 100 000 less potent than 17β-estradiol in the E-screen assay.

4.1.2.9.2 Fertility

Studies in animals

The evaluation of effects on fertility following exposure to ptBP is based on a combined repeated dose and reproductive/developmental screening test acording to OECD 422 and a recent 2-generation reproduction toxicity test according to OECD Guideline 416.

In the OECD combined repeated dose and reproductive/developmental toxicity screening test (OECD 422) conducted according to GLP groups of male and female Sprague-Dawley rats (13/sex/dose) received daily doses of ptBP via oral gavage at doses of 0, 20, 60, and 200 mg/kg bw/day for approximately 6 weeks, including pregnancy and a 4-day post partum period in females (MHW, 1996). Dosing was from 14 days before mating to 14 days after mating for males and from 14 days before mating until day 3 of lactation in females. As vehicle a 0.5% methyl cellulose solution was used. *Results:* At 200 mg/kg bw/day one female from the F0 generation was found dead two days after delivery. Five of the 16 newborns from this dam were found dead on the delivery day. The other 11 newborns were dead on the first day of delivery. Gross necropsy of the dam showed sub involution and change in colour (red or black) in the lungs. Histopathologic examination revealed congestion in the lungs. However, this was considered to be an administration mistake. Furthermore, at 200 mg/kg bw/day some females showed stridor associated with dyspnea, likely caused by irritation of the respiratory tract. This may be related to a secondary effect due to gavage application of an irritating material. There was no significant difference in the number of corpora lutea, number of implantation sites, in the number of pups born, delivery index, number of pups alive, birth index, and live birth index between the control animals and the exposed animals. The plasma concentration of albumin in the males was slightly decreased, accompanied by decrease in plasma protein. A significant decrease in red blood cells and white blood cells in males in the 200 mg/kg bw/day dose group was also reported. No compound related morphological changes were observed during pathological examination of parental animals. There were no treatment related toxic effects in pregnant and lactating females other than respiratory

irritation. The NOAEL for systemic toxicity in the parental generation is considered to be 60 mg/kg bw/day as discussed in chapter 4.1.2.6 – "repeated dose toxicity". The NOAEL for effects on fertility was ≥ 200 mg/kg bw/day. The study was performed in compliance with GLP.

A 2-generation reproduction study in Sprague-Dawley rats with ptBP was performed according to OECD Guideline 416 and US EPA Guideline OPPTS 870.3800, and in compliance with GLP (Clubb and Jardine, 2006). PtBP was given orally in the diet at the following doses 0, 800, 2500 and 7500 ppm, corresponding to approximately 70, 200 and 600 mg/kg bw/day. In the F0 generation 28 rats/sex/group were used and in the F1 generation 24/sex/group. The results were as following: **F0 generation:** No treatment related clinical signs were reported. There were no clear effects of treatment on mating performance, fertility or duration of gestation in the F0 generation. A statistically significant decrease in body weight gain was reported in F0 males from week 0 to16 of the study at 2500 ppm (324 vs 351g in controls) and at 7500 ppm (252 vs 351g in controls), and in F0 females at 2500 ppm (95 vs 114g in controls) and at 7500 ppm (78 vs 114g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (372 vs 441g in controls), and the body weight gain was 108 vs 138g in controls. The body weight during lactation at 7500 ppm was 321 vs 353g in controls. No statistically significant changes in body weights were reported at 800 ppm in males and females. At 7500 ppm food consumption was statistically significant reduced in F0 males from week 1 to week 16 of treatment (week 1; 20.3 vs 28.7 g/animal/day in controls, week 16; 28.5 vs 31.6 g/animal/day in controls), and in F0 females from week 1 to week 10 of treatment, prior to mating (week 1; 13.7 vs 20.6 g/animal/day in controls, week 10; 20.0 vs 22.8 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F0 females was 30.4 vs 33.0 g/animal/day in controls, and during lactation 75.8 vs 91.6 g/animal/day in controls. At 2500 ppm a statistically significant reduction in food consumption was reported in males at week 3 (29.3 vs 31.2 g/animal/day in controls) and week 14 (29.5 vs 31.4 g/animal/day in controls) of treatment. In females a statistically significant reduction in food consumption was reported in 6 of 10 weeks of treatment, prior to mating (week 1; 17.5 vs 20.6 g/animal/day in controls, week 10; 21.3 vs 22.8 g/animal/day in controls). No statistically significant changes in food consumption were reported at 800 ppm in males and females. At 7500 ppm a statistically significant increase in the weights of the kidneys (4.29 vs 3.96 g in controls) and liver (20.19 vs 18.87 g in controls) in males was reported, and in females a statistically significant decrease in the weight of the adrenal gland (0.064 vs 0.076 g in controls), ovaries (0.081 vs 0.107g in controls) and pituitary gland (0.011 vs 0.012g in controls) were reported following covariance analysis with the body weight as the covariate. At 2500 ppm a statistically significant decrease in the weights of the adrenal gland (0.070 vs 0.079g in controls) and ovaries (0.095 vs 0.109 g in controls) were reported in females. No changes in organ weights were reported at 2500 ppm in males and at 800 ppm in males and females. At 7500 ppm in F0 females an increase in the incidence of primordial follicles (120 ± 53 vs 102 ± 44 in controls) with a concurrent decrease in the incidence of growing follicles (80 ± 29 vs 96 ± 30 in controls) was reported, however this effect was more pronounced in the F1 generation. Furthermore, F0 females at 7500 ppm had a statistically significant increase in atrophy of the vaginal epithelium with 12/28 rats affected and the severity of the findings was 5 with minimal atrophy and 7 with mild atrophy. At 2500 ppm 7/28 females had atrophy of the vaginal epithelium and the severity of the findings was 3 with minimal atrophy and 4 with mild atrophy. At 800 ppm 2/28 had minimal atrophy of the vaginal epithelium, and 1/28 in the control group with minimal atrophy. In F0 females at 7500 ppm there was statistically significant greater incidence of females that were in pro-esterus (14 vs 6 in controls), and a

lower incidence of females in meto-estrus (2 vs 13 in controls). In F0 males no significant effects on sperm motility, sperm count or sperm morphology were reported. No statistically significant effects on implantation, litter size and litter weights were reported at 800 ppm. At 7500 ppm a slight decrease in the number of implantation sites (13.1 ± 2.0 vs 14.4 ± 3.1 in controls) and live pups born/litter (12.2 ± 2.0 vs 13.1 ± 2.8 in controls) were reported. The litter size was slightly smaller compared to controls (12.3 ± 2.0 vs 13.4 ± 3.0 in controls), and the litter weight was lower than controls at 7500 ppm (LD 1: 72 ± 14 vs 80 ± 12g in controls, and LD 21: 424 ± 102 vs 598 ± 79g in controls). Litter weight gain was similarly affected. At 2500 ppm pup body weights and litter weights were also reduced from LD 14 (324 ± 83 vs 357 ± 52g in controls). In addition at 7500 ppm pup survival was reduced particularly over days 1-4 of lactation where 6 different litters had more than 3 pups dying, and in 2 of these litters all pups died. **F1 generation**: No treatment related clinical signs were reported. There were no clear effects of treatment on mating performance, fertility or duration of gestation in the F1 generation. A statistically significant decrease in body weight gain was reported in F1 males from week 4 to 22 of the study at 7500 ppm (357 vs 442g in controls), and in F1 females from week 4 to 15 (prior to mating) at 7500 ppm (143 vs 173g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (320 vs 411g in controls). The body weight gain during gestation in F1 females at 7500 ppm was 89 vs 130g in controls. The body weight during lactation at 7500 ppm was 290 vs 335g in controls. At 2500 ppm statistically significant changes in body weights in males were reported from week 4 (114 vs 124 in controls) to week 9 (358 vs 379 in controls) of treatment. No statistically significant changes in body weights were reported at 2500 ppm in females and at 800 ppm in males and females. At 7500 ppm food consumption was statistically significant reduced in F1 males from week 5 to week 22 of treatment (week 5; 20.1 vs 23.6 g/animal/day in controls, week 22; 26.0 vs 32.2 g/animal/day in controls), and in F0 females from week 5 to week 15 of treatment (prior to mating) (week 5; 17.4 vs 19.2 g/animal/day in controls, week 15; 19.0 vs 23.7 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F1 females was 26.2 vs 30.9 g/animal/day in controls, and during lactation 69.9 vs 91.1 g/animals/day in controls. At 2500 ppm a statistically significant reduction in food consumption was reported in females at week 13 (21.8 vs 23.1 g/animal/day in controls) and week 15 (21.9 vs 23.7 g/animal/day in controls) of treatment (prior to mating). No statistically significant changes in food consumption were reported at 2500 ppm in males and at 800 ppm in males and females. At 7500 organ weight changes in weanling animals included a decreased spleen weight in males (0.26 vs 0.29 g in controls) and females (0.24 vs 0.27 g in controls) at 7500 ppm following covariance analysis with the body weight as the covariate. Furthermore, in F1 females at 7500 ppm statistically significant decreases in the weights of the adrenal gland (0.059 vs 0.076 g in controls), ovaries (0.075 vs 0.104 g in controls), pituitary gland (0.011 vs 0.013 g in controls), brain (1.84 vs 1.89g in controls), kidney (2.32 vs 2.52g in controls) and uterus (0.48 vs 0.67 g in controls) were reported when compared to controls, as well as a significant increase in liver weight (18.47 vs 16.18 g in controls) following covariance analysis with the body weight as the covariate. At 2500 ppm a statistically significant decrease in the weights of the adrenal gland (0.068 vs 0.076 g in controls) and brain (1.84 vs 1.89 g in controls) were reported in F1 females when compared to controls, and the liver weight was significantly increased (17.35 vs 16.18 g in controls) when compared to controls following covariance analysis with the body weight as the covariate. No changes in organ weights were reported at 800 ppm in males and females. At 7500 ppm in F1 females an increase in the incidence of primordial follicles (134 ± 55 vs 79 ± 35 in controls) with a concurrent decrease in the incidence of growing follicles (64 ± 13 vs 80 ± 30 in controls) was reported. This effect was more pronounced in the F1 generation compared to the F0 generation. In F1 females at 7500 ppm an increase in atrophy of the vaginal epithelium

was reported compared to control animals, with the severity being mild in 10/24 of the animals and minimal in 4/24 of the animals, with a total of 14/24 affected. The severity in the atrophy of the vaginal epithelium was more pronounced in the F1 generation compared to the F0 generation. No increase in atrophy of the vaginal epithelium was reported at the lower doses. The severity in F1 females increased compared to F0 females. In F1 males no significant effects on sperm motility, sperm count or sperm morphology were reported. In the F1 generation the number of implantation sites (11.6 ± 1.3 vs 14.4 ± 1.9 in controls at 7500 ppm) and live pups born/litter (10.8 ± 1.8 vs 13.5 ± 2.6 in controls at 7500 ppm) was much more variable compared to the F0 generation, however, the survival of these smaller litters was normal. After LD 1 pup body weight was lower than controls (62 ± 9 vs 78 ± 14 in controls), and by LD 21 the body weight was approximately 25 - 30% lower than control weights (395 ± 51 vs 554 ± 146 in controls). Litter weight gain was similarly affected. At 7500 ppm vaginal opening and preputial separation occurred 3 and 4 days later than controls, respectively. The weight of the female pups at vaginal opening was 120 ± 13 in controls and 122 ± 11 at 7500 ppm, and in male pups at preputial separation 220 ± 20 in controls and 205 ± 20 at 7500 ppm. The effect on preputial separation may be related to the lower body weights of the male pups. No effects on anogenital distance and nipple retention were reported. **F2 generation:** No effects on survival of the pups. At 7500 ppm a slightly smaller litter size and reduced litter weight was reported at LD 1. Pup weight gain was lower than controls, and at LD 20 the weight gain was 20% less than controls. At 2500 ppm the pup weight was lower than controls from LD 14, with a concurrent decrease in litter weight gain as well. The NOAEL for effects on reproductive organs/fertility was set at 800 ppm corresponding to 70 mg/kg bw/day. The NOAEL value was based on a statistically significant decrease in the relative weight of the ovary in the F0 and F1 generation from 2500 ppm, and an increase in vaginal epithelial atrophy compared to control animals from 2500 ppm in F0 females. An increase in vaginal epithelial atrophy compared to control animals was also reported in the F1 generation at 7500 ppm, and the severity of the vaginal epithelium atrophy was more pronounced in the F1 generation compared to the F0 generation.

4.1.2.9.3 Developmental toxicity

Studies in animals

No data from a developmental toxicity study according to OECD 414 are available. However, a recently performed 2-generation study is available as well as an OECD 422 Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test.

The results from an OECD 422 Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test indicate that ptBP is not embryotoxic or teratogenic at the doses tested (0, 20, 60 and 200 mg ptBP/kg bw/day). Examination of body weights and gross morphology of the offspring revealed no effects of ptBP, and there were no significant differences in the viability index day 4 of lactation between the control animals and the exposed animals. However, at 200 mg/kg bw/day one female from the F0 generation was found dead two days after delivery. Five of the 16 newborns from this dam were found dead on the delivery day. The other 11 newborns were dead on the first day of delivery. There were no morphological abnormalities in the newborns that were dead on the day of delivery. Furthermore, no abnormalities were found in the newborns that underwent necropsy on day 4 of post partum. Gross necropsy of the dam showed sub involution and change in colour (red or black) in the lungs. Histopathologic examination revealed congestion in the lungs.

However, this was considered to be an administration mistake.Overall, no treatment related toxic effects on offspring were reported and a NOAEL of ≥ 200 mg/kg/day for developmental toxicity was identified. For maternal toxixity a NOAEL at 60 mg/kg bw/day was identified based on the observation that some females showed stridor associated with dyspnea in the 200 mg/kg bw/day dose group. However, this was likely caused by irritation of the respiratory tract, and may be related to a secondary effect due to gavage application of an irritating material. For further study description see section 4.1.2.9 Fertility.

A 2-generation reproduction study in Sprague-Dawley rats with ptBP was performed according to OECD Guideline 416 and US EPA Guideline OPPTS 870.3800 (Clubb and Jardine, 2006). ptBP was given orally in the diet at the following doses 0, 800, 2500 and 7500 ppm, corresponding to approximately 70, 200 and 600 mg/kg bw/day. In the F0 generation 28 rats/sex/group were used and in the F1 generation 24/sex/group. The full study description is given in section 4.1.2.9.2 Fertility. The results regarding developmental effects were as following: **F0 generation:** No treatment related clinical signs were reported. A statistically significant decrease in body weight gain was reported in F0 females at 2500 ppm (95 vs 114g in controls) and at 7500 ppm (78 vs 114g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (372 vs 441g in controls), and the body weight gain was 108 vs 138g in controls. The body weight during lactation at 7500 ppm was 321 vs 353g in controls. No statistically significant changes in body weights were reported at 800 ppm in females. At 7500 ppm food consumption was statistically significant reduced in F0 females from week 1 to week 10 of treatment, prior to mating (week 1; 13.7 vs 20.6 g/animal/day in controls, week 10; 20.0 vs 22.8 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F0 females was 30.4 vs 33.0 g/animal/day in controls, and during lactation 75.8 vs 91.6 g/animals/day in controls. In females a statistically significant reduction in food consumption was reported in 6 of 10 weeks of treatment, prior to mating (week 1; 17.5 vs 20.6 g/animal/day in controls, week 10; 21.3 vs 22.8 g/animal/day in controls). No statistically significant changes in food consumption were reported at 800 ppm in females. At 7500 ppm the litter weight was lower than controls at 7500 ppm (LD 1: 72 ± 14 vs 80 ± 12g in controls, and LD 21: 424 ± 102 vs 598 ± 79g in controls). Litter weight gain was similarly affected. At 2500 ppm pup body weights and litter weights were also reduced from LD 14 (324 ± 83 vs 357 ± 52g in controls). In addition at 7500 ppm pup survival was reduced particularly over days 1-4 of lactation where 6 different litters had more than 3 pups dying, and in 2 of these litters all pups died. **F1 generation**: No treatment related clinical signs were reported. A statistically significant decrease in body weight gain was reported in F1 females from week 4 to 15 (prior to mating) at 7500 ppm (143 vs 173g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (320 vs 411g in controls). The body weight gain during gestation in F1 females at 7500 ppm was 89 vs 130g in controls. The body weight during lactation at 7500 ppm was 290 vs 335g in controls. At 7500 ppm food consumption was statistically significant reduced in F0 females from week 5 to week 15 of treatment (prior to mating) (week 5; 17.4 vs 19.2 g/animal/day in controls, week 15; 19.0 vs 23.7 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F1 females was 26.2 vs 30.9 g/animal/day in controls, and during lactation 69.9 vs 91.1 g/animal/day in controls. At 2500 ppm a statistically significant reduction in food consumption was reported in females at week 13 (21.8 vs 23.1 g/animal/day in controls) and week 15 (21.9 vs 23.7 g/animal/day in controls) of treatment (prior to mating). After LD 1 pup body weight was lower than controls (62 ± 9 vs 78 ± 14 in controls), and by LD 21 the body weight was approximately 25 - 30% lower than control weights (395 ± 51 vs 554 ± 146 in controls) at 7500 ppm. Litter weight gain was similarly affected. At 7500 ppm vaginal opening and preputial separation occurred 3 and 4 days later than controls,

respectively. The weight of the female pups at vaginal opening was 120 ± 13 in controls and 122 ± 11 at 7500 ppm, and in male pups at preputial separation 220 ± 20 in controls and 205 ± 20 at 7500 ppm. The effect on preputial separation may be related to the lower body weights of the male pups. No effects on anogenital distance and nipple retention were reported. **F2 generation:** No effects on survival of the pups. At 7500 ppm a slightly smaller litter size and reduced litter weight was reported at LD 1. Pup weight gain was lower than controls, and at LD 20 the weight gain was 20% less than controls. At 2500 ppm the pup weight was lower than controls from LD 14, with a concurrent decrease in litter weight gain as well. The NOAEL for developmental toxicity was set at 800 ppm corresponding to 70 mg/kg bw/day from this study, and will be used in the risk characterisation. The NOAEL value for offspring was based on a reduced pup body weight and litter weight from LD 14 from 2500 ppm in the F1 generation, and F2 generation. At this dose level no statistically significant reduction in maternal body weight during gestation or lactation was reported. The NOAEL for maternal toxicity was 800 ppm and was based on a statistically significant decrease in body weight gain in F0 females at 2500 ppm from week 1-16 of the study as well as a statistically significant reduction in food consumption in F0 and F1 females before mating. A statistically significant reduction in ovary weight and adrenal gland weight was also reported at 2500 ppm.

In a study by Haavisto et al., 2003 the effects of ptBP, ptOP and diethylstilbestrol (DES) on prenatal testicular testosterone surge in the Sprague-Dawley rat was evaluated at embryonic day (ed) 19.5. *In utero* exposure by subcutaneous injection to ptBP (13 dams) or ptOP (25 dams) at doses of 1.0, 10 and 100 mg ptBP/kg bw and doses of 0.1, 1.0, 10 and 100 mg ptOP/kg bw on ed 13.5, 15.5 and 17.5 did not decrease testicular testosterone content, whereas exposure to DES (18 dams, 0.01, 0.1, or 0.2 mg/kg bw) caused a significant depression in testosterone content and secretion. Nine dams were used in the control group. *In utero* exposure to the alkylphenols had no effect on foetal body weight gain. The NOAEL for changes in testosterone surge was ≥100 mg/kg bw for ptBP, the highest concentration tested. The *in vivo* results were further evaluated in ex *in v*ivo tissue cultures of intact ed 19.5 testes. The basal testosterone and progesterone secretion was determined during, and after a 3-hours culture period. PtBP (100 mg/l) and ptOP (10, 100 and 500 mg/l) significantly increased testosterone and progesterone secretion by up to seven fold, whereas DES (100 mg/l) did not alter testosterone secretion but caused a two-fold increase in progesterone secretion. However, in the presence of 100 mg/l ptBP the intratesticular testosterone content did not correlate with the significantly increased fraction of secreted or leaked testosterone. The latter was correlated with tissue damage observed at the electron microscopic level. At 500 mg/l ptBP the secretion of testosterone decreased to control value, whereas the secretion of progesterone remained 1.9 fold elevated. At the electron microscopic level both ptBP and ptOP caused severe changes in Leydig cell membrane structures and lipid droplets. In the DES treated testes membrane vesicle formation around the lipid droplets and increased mitochondrial pleiomorphy were reported. The conclusion of the study made by the authors was that alkylphenols have less severe and even opposite *in utero* effects on the prenatal rat testicular testosterone steroidogenesis when compared with the effect of DES which induced a significant depression of testosterone content. The tissue damage reported is considered related to ptBP exposure, however, this was observed after *in vitro* exposure, and since no effect on the prenatal testosterone surge was reported following *in utero* exposure, the effect reported *in vitro* is considered as additional information.

4.1.2.9.4 Summary of toxicity for reproduction

The studies available are a recent OECD 416 two-generation reproduction toxicity study and an OECD 422 Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test. In the 2-generation reproduction study rats were exposed to ptBP in the diet at the following doses 0, 800 2500 and 7500 ppm corresponding to approximately 0, 70, 200 and 600 mg/kg bw/day. The following results were reported: From 2500 ppm a statistically significant decrease in weight gain was reported in F0 and F1 animals prior to mating. During gestation and lactation a statistically significant reduciton in body weight gain was reported at 7500 ppm A statistically significant reduction in food consumption was reported as well from 2500 ppm in F0 and F1 animals prior to mating. During gestation and lactation a statistically significant reduciton in food consumption was reported qt 7500 ppm.At concentrations up to 7500 ppm no effects on mating performance, fertility or duration of gestation were reported. However, at 7500 ppm a slight decrease in the number of implantation sites, live pups born and viability of the pups were reported. Furthermore, a decrease in pup body weights and litter weights in the F1 and F2 generation from 2500 ppm was reported on LD 14, as well as a smaller litter size. Pup survival was reduced particularly over days 1-4 of lactation were 6 different litters had more than 3 pups dying, and in 2 of these litters all pups died. A delay in vaginal opening and preputial separation in the F1 generation was reported as well at 7500 ppm. In the F0 and F1 female generation a marked increase in atrophy of the vaginal epithelium was reported from 2500 ppm. The severity in the vaginal epithelium atrophy in the F1 generation increased compared to the F0 generation. In the F0 and F1 females at 7500 ppm an increase in the incidence of primordial follicles with a concurrent decrease in the incidence of growing follicles were reported as well. This effect was also more pronounced in the F1 generation. From 2500 ppm a statistically significant decrease in the weight of the ovaries was reported in the F0 generation, however, only at 7500 ppm in the F1 generation. A NOAEL at 800 ppm corresponding to 70 mg/kg bw/day was derived for effect on reproduction and development from the 2-generation study.

The results from the Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test (OECD 422) indicated that ptBP had no effect on fertility and induced no embryotoxicity or teratogenicity at the dose levels tested (0, 20, 60 and 200 mg/kg bw/day). The NOAEL for fertility and developmental toxicity derived from this study was ≥ 200 mg/kg bw/day.

In *in vitro* studies ptBP was shown to have a weak estrogenic activity. A possible anti-androgen activity of ptBP has not been elucidated.

A NOAEL value at 800 ppm corresponding to 70 mg/kg bw/day from the 2-generation reproduction toxicity study will be put forward to the risk characterisation for effects on fertility and development.

4.1.3 Risk characterisation [9]

4.1.3.1 General aspects

The human population may be exposed to ptBP at the workplace, from the use of consumer products and indirectly via the environment.

Occupational exposure may find place during production of ptBP or when ptBP is used as a chemical intermediate when plastic polymers (polycarbonate, phenolic or epoxy resins) are synthesised. End use of the resins (paints, glues) may also give raise to exposure.

Potential consumer exposure is via direct use of products with phenolic resins or epoxy resins containing residual ptBP monomers, or via use of the final product containing residual concentration of ptBP. The main exposure from final products is expected to be from adhesives and possibly canned food. Consumers may also be exposed to ptBP in drinking water from drinking water reservoirs or pipelines and from polycarbonate used for food contact material. Some exposure may also occur from various consumer articles such as cosmetics, eyeglass frames, tooth and hair brushes, hearing aids, however, exposure from these products are considered to be low. The main routes of exposure to consumer products are by dermal contact (e.g. use of adhesives) and by ingestion of food products into which ptBP have migrated from the food/water container or packaging (e.g. food contact applications). For humans exposed indirectly from the environment, the main exposure is expected to be from ingestion.

The excretion of ptBP via feces and urine as well as the retention of the material in certain tissues was assessed in rats exposed to ptBP by the oral route. The results showed that 26.7 % and 72.9 % of the applied dose were eliminated via feces and urine, respectively. In another *in vivo* rat study where ptBP was injected intraveneously 65 – 75% and 17 – 21% of the applied dose was excreted as glucuronide and sulphate conjungates, respectively. The total recovery of radioactivity was 91 –93 %. This indicates that the glucuronidation pathway is most prevalent. *In vitro* studies with rat hepatocytes and human liver cells supported the results of the *in vivo* rat study with intraveneously applied ptBP. The retention of ptBP in rats after 7 days was 0.1% and can therefore be regarded as negligible. The results of the rat studies clearly indicate that ptBP is rapidly excreted. The likelihood for accumulation is therefore considered as low.

The urinary metabolite levels in workers handling ptBP showed an increasing level of ptBP metabolites in the urine with increasing exposure to ptBP. Most of the ptBP was excreted within 24 hours. This indicates that skin penetration plays an important role as a route of entry in addition to vapour exposure.

In the risk characterisation, 100% absorption is used for oral exposure. This is based on the study by Freitag et al., where 26.7% and 72.9% of the orally applied dose were eliminated via feces and urine, respectively. In this study there was no information whether the faeces

[9] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

derived radioactivity stems from metabolites or unabsorbed ptBP. However, in the study by Koster et al., 1981 nearly 100 % of the intravenous applied dose was excreted as conjugated metabolites, it is not known how much of the dose that was excreted in the bile and how much was excreted via urine. Therefore, this study as such cannot be used for estimation of absorption figures. Furthermore, absorption of nearly 100 % is expected since ptBP has a low molecular weight (152), low $logP_{ow}$ value (3.31) and high solubility in water (600 mg/l). In the absence of data on the percentage absorption by inhalation, a default value of 100 % is used for inhalation exposure. For dermal exposure no studies are available, however, related to the water solubility (600 mg/l), a $logP_{ow}$ value at 3.31 and low molecular weight (152) for ptBP an absorption of 100% is considered used for ptBP (according to the criteria in the TGD, Appendix IV, p. 263).

PtBP appears to have low acute toxicity by all three exposure routes. A limit test gives a LC_{50} for inhalation above 5600 mg/m^3 (dust aerosol) with an additional vapour component of 30 mg/m^3. Most studies shows dermal and oral LD_{50} values above 2000 mg/kg bw. The exception is an oral study where high and increasing doses of vehicle (DMSO) is likely to have influenced the toxicity reported.

PtBP is shown to be moderately to severely irritating to skin, eyes and the respiratory system. The data support the classification as Xi; R37/38-41 even though some studies report necrosis and corrosivity in a minority of the ptBP-exposed animals.

PtBP might be a sensitiser in humans. Of the three animal studies reported two studies, performed according to OECD 406 and GLP is negative, and the other, an older non-GLP, non-guideline study, is positive. The database for assessing human skin sensitisation for ptBP is limitated.

The repeated dose toxicity studies available are an OECD combined repeated dose and reproductive/developmental toxicity screening test (OECD 422), a 2-generation reproduction toxicity study (OECD 416), and several depigmentation studies. The highest dose used in the OECD 422 study was 200 mg/kg bw/day, which was considered a LOAEL for systemic toxicity due to moderate haematological effects in males. The NOAEL from this study was 60 mg/kg bw/day (MHW, 1996). The respiratory stress noted in the high dose females in this study might be related to local toxicity during repeated feeding by oral gavage. The severity of the changes observed in blood parameters in males is questionable. In the 2-generation reproduction toxicity study in Sprague-Dawley rats with ptBP (Clubb and Jardine, 2006) ptBP was given orally in the diet (0, 800, 2500 and 7500 ppm, corresponding to approximately 0, 70, 200 and 600 mg/kg bw/day). From this study a NOAEL at 70 mg/kg bw/day was derived based on reduced relative weights of ovaries and adrenal glands in females as well as an increase in vaginal epithelium atrophy.

There are several human and animal studies evaluating the depigmentation potential of ptBP. There are conflicting results in these studies and there is a discussion within the scientific community regarding possible false positives and false negatives in the human studies due to the use of different solvents and lack of proper controls. However, overall there seems to be evidence that ptBP can cause depigmentation in humans that are supported by animal studies. In animals ptBP induced skin depigmentation both locally and systemic. In an oral study (Hara et al., 1969) ptBP induced skin depigmentation in black mouse (5 mice/group). The lowest dose with a positive reaction was after oral exposure to 6 mg ptBP 3times/week in 6 month. This gives a *systemic* LOAEL for animals at103 mg/kg bw/day. Animal studies have shown depigmentation after patch test with 10 mg ptBP both in DMSO and propylene glycol

as solvents, while human studies have shown depigmentation at concentrations ≥ 50% ptBP. There are some studies in humans showing depigmentation at 2% ptBP. The depigmentation is reversible after some months when the inducing material is removed from the skin. A human LOAEL of 0.0086 to 0.014 mg/kg bw is suggested. However, this LOAEL value is not based on repeated exposure to ptBP, and the humans used in the patch test was occupationally exposed to ptBP. The systemic LOAEL for depigmentation at 103 mg/kg will be used in the risk characterisation.

In the risk characterisation for repeated dose toxicity a systemic NOAEL at 70 mg/kg bw/day from the recent 2-generation reproduction toxicity study by Clubb and Jardine, 2006, will be used. This is a study performed in accordance with accepted OECD test guidelines and in compliance with GLP, and the effects reported in this study are considered more relevant to humans than the effects reported in the OECD 422 screening study. As regard the *systemic* LOAEL at 103 mg/kg bw/day based on depigmentation in C75 black mice, this value will be put forward to the risk characterisation. We will also forward the NOAEL value at 70 mg/kg bw/day from the repeted dose toxicity study from the 2-generation reproduction toxicity study. In the risk characterisation we will use both the NOAEL and the LOAEL. The depigmentation study is an old study not performed in accordance with acceptable test guidelines and with few animals per test group, however, this study is directly relevant to depigmentation. The reason for using two different values for repeated dose toxicity and depigmentation is based on the fact that the systemic NOAEL is from a study with albino Sprague-Dawley rats in the 2-generation study. This strain of rats is not possible to use for detection of depigmentation. The systemic toxicity NOAEL of 70 mg/kg/day and will be forwarded to the risk characterisation for **all other aspects** than depigmentation.

P-tert-butylphenol (ptBP) was negative in three bacterial tests. The mouse lymphoma TK+/- locus assays have given both negative and positive results, apparently depending upon duration of exposure. One study performed according to OECD TG 476 and GLP was negative. Another study was also negative at the recommended exposure times while ptBP appeared to be mutagenic after 24 h exposure. PtBP induced chromosomal aberrations with an exogenous metabolic activation and polyploidy with and without an exogenous metabolic activation in two studies with Chinese hamster lung cells but not in a study with rat lymphocytes.Thus, the overall results regarding mammalian cell mutagenicity *in vitro* is inconclusive. To elucidate *in vivo* genotoxicity of ptBP, two mammalian erythrocyte micronucleus tests were conducted. No increase in the frequency of micronucleated bone marrow cells was observed in any dose group. Although not statistically significant, the data indicate that there is a trend to decreased PCE/NCE ratios with dose. In addition, the route of administration in combination with the tested dose (close to MTD) suggests that it is very likely that the material has reached the target organ.
Based on data from the other alkylphenols and the mutagenicity data on ptBP available, it is concluded that ptBP is most likely not mutagenic.

PtBP is not considered a human carcinogen. Based on the results from a rat study where only one papilloma of the forestomach was found and the absence of mutagenic effects, it is not likely that ptBP should be a human carcinogen. However, its ability to increase the frequency of squamous cell carcinomas in the rat forestomach following initiation with MNNG indicates that ptBP may act as a tumour promoter in rats. The available studies on carcinogenicity are not sufficient to assess to carcinogenic potential of ptBP, but as ptBP most probable is not mutagenic; it is unlikely that the substance is carcinogenic.

Regarding toxicity to reproduction effects on fertility as well as development will be addressed. Currently there is no prenatal developmental toxicity study according to OECD Guideline 414 available. The studies available are a recent OECD 416 two-generation reproduction toxicity study and an OECD 422 Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test. In the 2-generation reproduction study rats were exposed to ptBP in the diet (0, 800 2500 and 7500 ppm corresponding to approximately 0, 70, 200 and 600 mg/kg bw/day). The following results were reported: From 2500 ppm a statistically significant decrease in weight gain and reduced food consumption in F0 and F1 animals prior to mating. During gestation and lactation a slight decrease in body weight gain and food consumption was reported at 2500 ppm, that reached statistically significance at 7500 ppm. At concentrations up to 7500 ppm no effects on mating performance, fertility or duration of gestation were found. However, at 7500 ppm a slight decrease in the number of implantation sites, live pups born and viability of the pups were described. The decrease in implantation sites was more pronounced in the F1 generation. Furthermore, a statistically significant decrease in pup body weights and litter weights in the F1 and F2 generation from 2500 ppm was reported, and a slightly smaller litter size in the F1 generation at 7500 ppm. A delay in vaginal opening and preputial separation in the F1 generation was found as well at 7500 ppm, however, this may be related to the decreased pup body weight. In the F0 and F1 female generation a marked increase in atrophy of the vaginal epithelium was observed from 2500 ppm. The severity in the vaginal epithelium atrophy in the F1 generation increased compared to the F0 generation. In the F0 and F1 females at 7500 ppm an increase in the incidence of primordial follicles with a concurrent decrease in the incidence of growing follicles was observed as well. This effect was also more pronounced in the F1 generation compared to the F0 generation. At 2500 ppm and 7500 ppm a statistically significant decrease in the relative weight of the ovaries was found in the F0 generation, and in the F1 generation at 7500 ppm. A NOAEL at 800 ppm corresponding to 70 mg/kg bw/day was derived from this study for effect on reproduction and developmental toxicity.

In *in vitro* studies ptBP was shown to have a weak estrogenic activity. A possible anti-androgen activity of ptBP has not been elucidated.

Based on the results from the 2-generation reproduction toxicity study in rats a NOAEL at 800 ppm corresponding to 70 mg/kg/bw/day was derived for effects on reproduction, and is used in the risk characterisation for effects on fertility and development.

Table 4.40 The N(L)OAEL values for the concerned endpoints used in the calculation of the MOS values.

Endpoint	Study design	Critical effect	(N(L)OAEL)	Reference
Repeated dose toxicity (systemic)	C57 black mice; 5 mice/group; oral via gavage; 6 mg ptBP 3 times/week in 6 months	Depigmentation	6 mg ptBP 3 times/week in 6 months corresponding to 103 mg/kg bw/day	Hara et al., 1969
	Sprague-Dawley rats; 2-generation study (OECD 416); oral via diet; 0, 800, 2500 and 7500 ppm corresponding to 0,	Increased vaginal epithelium atrophy and reduced relative weight of ovaries and adrenal glands in females at 200 mg/kg bw/day	800 ppm corresponding to 70 mg/kg bw/day	Clubb and Jardine, 2006.

	70, 200 and 600 mg/kg bw/day			
Fertility	Sprague-Dawley rats; 2-generation study (OECD 416); 0, 800, 2500 and 7500 ppm corresponding to 0, 70, 200 and 600 mg/kg bw/day	F0: From 2500 ppm statistically significant decreased body weight gain and food consumption in males and females before mating. At 7500 ppm a statistically significant reduction in body weight gain during gestation and lactation. From 2500 ppm a statistically significant decrease in the relative weight of the ovary. From 2500 ppm statistically significant increase in atrophy of vaginal epithelium. At 7500 ppm increase in primordial follicles in F0 females with a concurrent decrease in growing follicles. At 7500 ppm increase in females in pro-estrus with a lower incidence of females in meto-estrus. At 7500 ppm a slight decrease in implantation sites and in live pups born/litter and in litter size as well as litter weight gain. F1: From 2500 ppm statistically significant decreased body weight gain in males, and in females at 7500 ppm. From 2500 ppm statistically significant decreased food consumption in females, and in males at 7500 ppm. At 7500 ppm increase in primordial follicles in F1 females with a concurrent decrease in growing follicles. This effect was more pronounced in the F1 generation compared to the F0 generation. At 7500 ppm statistically significant increase in atrophy of vaginal epithelium. This effect was more pronounced in the F1 generation compared to the F0 generation. At 7500 ppm a statistically significant decrease in the relative weight of the ovary. At 7500 ppm a slight decrease in implantation sites and in live pups born/litter and in litter size as well as litter weight gain.	800 ppm corresponding to 70 mg/kg bw/day	Clubb and Jardine, 2006
Developmental toxicity	Sprague-Dawley rats; 2-generation study (OECD 416); 0, 800, 2500 and 7500 ppm corresponding to 0, 70, 200 and 600 mg/kg bw/day	*Maternal toxicity:* F0: From 2500 ppm statistically significant decreased body weight gain and food consumption in females from week 1-16 of the study. At 7500 ppm a statistically significant decrease in maternal body weight gain during gestation and lactation F1: At 7500 ppm statistically significant decreased body weight gain in females. From 2500 ppm statistically significant decreased food consumption in females before mating. For further information see repeated dose toxicity. *Developmental toxicity:* From 2500 ppm a statistically significant decrease in pup bw and litter weight in	Maternal toxicity: 800 ppm corresponding to 70 mg/kg bw/day. Developmental toxicity: 800 ppm corresponding to 70 mg/kg bw/day	Clubb and Jardine, 2006

		F1 and F2 , and at 7500 ppm a smaller litter size in F1 and F2 and an increase in pup mortality and decrease in pup viability in F1. At 7500 ppm a delay in vaginal opening and preputial separation in F1 (not measured in F2).		

[click here to insert table note or Table X.X continued overleaf or delete if not appropriate]

4.1.3.2 Workers

The main routes of exposure for workers are expected to be by inhalation and dermal contact. Ingestion is not considered to be relevant for occupational exposure. Exposure may find place during production of ptBP, when ptBP is used as a chemical intermediate or when professionals use resins and paints. PtBP will be handled and used both in molten and solid form and workers might be exposed to vapour, liquid or dust. The highest exposure levels are expected when performing processes at high temperatures, when handling dust or when resins are manually handled or used in working operations creating aerosols.

A summary of the exposure values is presented in table 4.24 and will be used in the risk characterisation of ptBP.

Based on submitted information from industry PPE is strictly applied by down stream users as recommended in the material safety data sheets (MSDS): To calculate the MOS-values for the concerned endpoints the NOAEL-value for the respective endpoints (table 4.41) are divided by the external or internal exposure. The internal exposure from the inhalation route is estimated by the formula below, where the parameters used is given in table 4.42. Data on absorption after inhalation is lacking. Therefore, 100 % respiratory absorption is used as a default value.
The dermal exposure is estimated by EASE for some scenarios (see section 4.1.1.2.). The internal exposure from the dermal route is considered to be 100 % of the exposure as a worst case estimate, divided with a bodyweight of 70 kg.

$$U_{inh} = \frac{B_{inh} * C * V_{inh}}{Bw}$$

Table 4.41 The parameters used in the formulas for estimating internal exposure by the inhalatory route

Symbol	Description	Value	Unit
U_{inh}	Internal exposure by the inhalatory route		mg/kg bw/day
B_{inh}	Bioavailability for inhalation exposure	1 (100%)	
C	Air concentration	-	mg/m^3
V_{inh}	Inhalation rate	10	m^3/day
BW	Body weight of a worker	70	kg

Table 4.42 Internal exposure calculated from external exposure (taken forward from chapter 4.1.1.2)

Exposure scenario	Inhalation		Dermal		Combined route
	External exposure	Internal exposure	External exposure	Internal exposure (with PPE)	Internal exposure (with PPE)
	mg/m^3	mg/kg/day	mg/day	mg/kg/day	mg/kg/day
Scenario I: Production of ptBP, highest measured/modelled TWA-values.					
RWC,TWA (product packers)	0.76	0.11	negligible		
Typical concentration	0.39	0.056	negligible		
RWC,Short term (sampling)	19	negligible[a]	negligible		
Typical concentration	7.3	negligible[a]	negligible		
Scenario II: Formulation and Processing					
II.1 RWC, TWA production of polycarbonate resins	0.014	0.002	negligible		
RWC, Short term (Unloading ptBP from ISO tanks)	0.6	0.09:8 = 0.01125[b]	negligible		
Typical concentration	0.11	0.015:8=0.001875[b]	negligible		
II.2 RWC, TWA production of phenolic resins	0.6	0.09	negligible		
II.3 RWC, TWA production of epoxy resins	6.6	0.94	420	6 (0.6)	6.94 (1.54)
Scenario III: End use scenarios					
III.1RWC, TWA, use of polycarbonate	<0.01	≤0.001	negligible		
III.2RWC, TWA use of phenolic resin (Handling uncured glue)	12	1.7	33.6	0.48 (0.048)	2.18 (1.748)
(Spray painting)	2.4	0.34	50	0.7 (0.07)	1.04 (0.41)
III.3RWC, TWA, use of epoxy resin	93	13.3	510	7.3 (0.73)	20.6 (14)
(Tank spraying) RWC	5.6	0.8	3600	51.4 (5.14)	52.2 (5.9)
(Tank spraying) Typical concentration	5.6	0.8	1020	14.6 (1.46)	15.4 (1.54)
III.4RWC, TWA, use of rubber additive	0.09	0.01	0.13	0.002 (0.0002)	0.012 (0.01)

RWC=reasonable, worst case, TWA= time weighted average.

[a] Because of the short duration of exposure (6 x 1 min) this will be negligible
[b] Calculated from 1 hour exposure / day

4.1.3.2.1 Acute toxicity

PtBP appears to have low acute toxicity by all exposure routes. A limit test gives a LC_{50} for inhalation above 5600 mg/m^3 (dust aerosol) with an additional vapour component of 30 mg/m^3. Most studies report dermal and oral LD_{50} values above 2000 mg/kg bw. The exception is an oral acute toxicity study where high and increasing doses of vehicle (DMSO) is likely to have influenced the toxicity reported.

Compared with the anticipated occupational exposure levels, 93 mg/m^3, it is concluded that ptBP is of no concern for workers with respect to acute effects (conclusion ii).

For dermal exposure the anticipated occupational exposure level is 7.3 mg/kg/day, and it is concluded that ptBP is of no concern for workers with respect to acute effects (conclusion ii).

4.1.3.2.2 Irritation and corrosivity

PtBP is regarded as severely irritating to skin, eyes and the respiratory system. Corrosive effects have also been reported. In addition PtBP may induce partial depigmentation of the skin (vitiligo, see section 4.1.3.2.4).

Skin

PtBP was found to be highly irritating to the skin in most recent studies conducted according to accepted guidelines. Since no threshold level (N(L)OAEL) has been identified for skin irritation, dermal exposure to liquid or solid will give raise to concern.

The producers of ptBP have informed that PPE is used regularly during production as specified in appendix A. A conclusion ii is drawn for scenario I production, dermal exposure. No new cases of skin depigmentation are reported since inproved occupational hygiene has been introduced.

Scenario II, production of phenolic resin and production of epoxy resins will be of concern. Industry reports the use of personal protective equipment (PPE) for these processes as detailed in Appendix A. A conclusion ii is drawn for scenario II.2 and II.3.

Scenario III.2, use of phenolic resins, scenario III.3, use of epoxy resins and scenario III.4, use of rubber additive (polymer) in uncured rubber, give raise to dermal exposure. Information on the use of PPE is specified in Appendix A. A conclusion ii is drawn for scenario III.2, III.3 and III.4.

Eye

PtBP has been shown to be highly irritating to the eyes and exposure to solid, liquid or vapour may give concern. No threshold level (N(L)OAEL) has been identified for eye irritation. The use of PPE is specified for scenario II.2, II.3, III.2, III.3 and III.4 in Appendix A and a conclusion ii is drawn for these scenarios.

Respiratory tract

PtBP has been shown to be irritating to the respiratory tract in animals, related to direct daily exposure of the tract. No threshold level (N(L)OAEL) has been identified for irritation of the respiratory tract. Since PPE has been specified for scenario II.2, II.3, III.2, III.3 and III.4 a conclusion ii is drawn for these scenarios.

4.1.3.2.3 Sensitisation

The database for assessing skin sensitisation has limitations. The human studies have major limitations in both number of test samples and mainly that the patients were suffering from former skin allergy or other skin diseases. Also the animal data are of varying reliability and the conclusion is drawn that ptBP does not fulfill the classification criteria as a sensitizer (Conclusion ii).

4.1.3.2.4 Repeated dose toxicity

The risk characterisation for repeated dose toxicity is discussed both for repeated dose toxicity in general and for (skin) depigmentation. The conclusions reached are listed in separate tables (table 4.43 a) and table 4.43 b)).

Repeated dose toxicity, general endpoints

A NOAEL of 800 ppm corresponding to a NOAEL of 70 mg/kg bw/day was concluded from a 2-generation reproduction toxicity study in Sprague-Dawley rats (OECD Guideline 416 and US EPA Guideline OPPTS 870.3800, Clubb and Jardine, 2006) This value is used in the risk characterisation both for repeated dose toxicity and reproductive toxicity (effects on fertility and development).

A minimal MOS is calculated from assessment factors based on default values given in the TGD draft from February 2005.

Interspecies: 10 (4(rat) x 2.5)

Intraspecies: 5 (standard for occupational)

Differences in duration of exposure: 1 (2-generation study)

Route to route extrapolation: 1 (accounted for before the calculation of the MOS)

Dose-response relationship: 1 (the starting point for the MOS calculation is a NOAEL)

Minimal MOS = 10x5= 50

The minimal MOS value is compared with the MOS values given in table 4.43a. This will give concern and conclusion iii for the following scenarios:

- II.3 Formulation and processing, Production of epoxy resins (dermal without PPE), (combined without PPE)
- III.2 End uses, Use of phenolic resins (inhalation) (combined, with and without PPE)

- III.3 End uses, Use of epoxy resins (inhalation) (dermal without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (RWC): (dermal, with and without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (typical conc): (dermal, with and without PPE) (combined, with and without PPE)

Due to lack of measured data, modelled data have been used for the estimation of the exposure values. Modelled exposure values are usually connected with high uncertainties and often regarded as conservative values (often higher levels than measured data). Especially the estimated levels of dermal exposure can be questioned. Since ptBP is a dermal irritant it is not likely to have an exposure period of long duration for concentrated solutions.

The producers of ptBP have informed that safety gloves and skin-cleansing agents are used during production as specified in Appendix A, and a conclusion ii is drawn for scenario I production, dermal exposure.

Industry informs that personal protective equipment (PPE) is used in the production of phenolic resin, and includes gloves and goggles for almost all operations with additional equipment like protective suits and respirators if necessary as specified in Appendix A and for dermal exposure a conclusion ii is drawn for scenario II.2 production of phenolic resin.

Epoxy resin producers inform that the workers wear gloves and dust/organic vapour mask as specified in Appendix A.

During spray painting workers typically wear PPE like air-purifying (filtered) or air-supplied respirators as well as gloves and protective coveralls to reduce exposure.

Depigmentation

There are some studies in humans showing depigmentation after exposure to 2 % ptBP in patch tests. A systemic LOAEL following oral administration of ptBP was calculated to be 103 mg/kg bw/day.(see section 4.1.2.6.6).

PtBP is absorbed via the respiratory tract and through intact skin in workers exposed occupationally. In a Japanese plant no new cases of skin depigmentation arose after improvement of the working conditions yielding an average excretion of ptBP in urine of about 2 mg ptBP/l urine in the highest exposed workers - the product packers. The product packers were exposed both by inhalation and through skin contact, but no information is available on the distribution between uptake via the respiratory tract and through intact skin (Ikeda et al., 1978). The German biological limit value in urine is based on this study. In a study the correlation between the 8 hours time weighted average (TWA)-values of ptBP in the working environment and the ptBP-excretion in urine from exposed workers was statistically significant (r=0.46), but its extent was weak (Kosaka et al., 1989).

The systemic LOAEL for mice (103 mg/kgbw/day) found by Hara et al., 1969 is used as the key study in the assessment of depigmentation as an endpoint. Conclusions for all scenarios and endpoints are given in Table 4.43 b).

A minimal MOS of 525 is derived using default factors for interspecies (17.5 (7 (mice) x 2.5)), intraspecies (5), differences in duration of exposure (2 (6 month study)), and dose-

response relationship 3 (the starting point for the MOS calculation is a LOAEL). This will give concern and conclusion iii for the following scenarios:

- II.3 Formulation and processing, Production of epoxy resins (dermal with and without PPE), (combined with and without PPE)
- III.2 End uses, Use of phenolic resins (inhalation) (dermal without PPE) (combined, with and without PPE)
- III.2 End uses, Use of phenolic resins, spray painting (inhalation) (dermal without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins: (inhalation) (dermal with and without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (RWC): (inhalation) (dermal, with and without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (typical conc): (inhalation) (dermal, with and without PPE) (combined, with and without PPE)

Table 4.43 a) Occupational risk assessment for repeated dose toxicity (min MOS = 50)

	Inhalation				Dermal				Combined			
	Exposure internal	NOAEL	MOS	Conclusion	Exposure Internal (with PPE)	NOAEL	MOS (with PPE)	Conclusion (with PPE)	Exposure (with PPE)	NOAEL	MOS (with PPE)	Conclusion (with PPE)
I. Production												
Product packers (highest measured TWA-value)	0.11mg/ kgbw/day	NOAEL: 70mg/ kgbw/day	636	ii	negligible			ii				ii
Typical concentration	0.056	70	1250	ii	negligible			ii				ii
Short term (both RWC and typical,)	negligible	70	-	ii	negligible			ii				ii
II. Formulation and processing												
Subscenario 1 Production of polycarbonate resins	0.002	70	35000	ii	negligible			ii				ii
RWC Short term	0.011	70	6363	ii	negligible			ii				ii
Subscenario 2 Production of phenolic resins	0.09	70	777.8	ii	negligible			ii (ii)				ii
Subscenario 3 Production of epoxy resins (1 h/day)	0.94:8= 0.12	70	583	ii	6 (0.6)	70	11.6 (116.7)	iii (ii)	6.12 (0.72)	70	11.4 (97)	iii (ii)
III. End uses												
Subscenario 1 Use of polycarbonate	≤0.001	70	70000	ii	negligible			ii (ii)				ii

	1.7	70	41.2	iii	0.48	70	146	ii	2.18	70	32.1	iii
Subscenario 2					(0.048)		(1458)	(ii)	(1.748)		(40.0)	(iii)
Use of phenolic resin	0.34		206	ii	0.7		100	ii	1.04		67.3	ii
Spray painting									(0.41)		170.7	(ii)
Subscenario 3	13.3	70	5.2	iii	7.3	70	9.6	iii	20.6	70	3.4	iii
Use of epoxy resin					(0.73)		(96)	(ii)	(14)		(5)	(iii)
Tank spraying, RWC	0.8		88	ii	51.4		1.4	iii	52.2		1.3	iii
					(5.14)		(13.6)	(iii)	(5.9)		(11.9)	(iii)
Tank spraying, typical concentration	0.8	70	88	ii	14.6	70	4.8	iii	15.4	70	4.5	iii
					(1.46)		(48)	(iii)	(1.54)		(0.45)	(iii)
Subscenario 4	0.01	70	7000	ii	0.002	70	35 000	ii	0.012	70	5833	ii
Use of rubber additive					(0.0002)		(350000)	(ii)	(0.01)		(7000)	(ii)

Table 4.43 b) Occupational risk assessment for repeated dose toxicity, depigmentation (min MOS = 525)

	Inhalation				**Dermal**				**Combined**			
	Exposure internal	**LOAEL**	**MOS**	**Conclusion**	**Exposure Internal (with PPE)**	**LOAEL**	**MOS (with PPE)**	**Conclusion (with PPE)**	**Exposure (with PPE)**	**LOAEL**	**MOS (with PPE)**	**Conclusion (with PPE)**
I. Production												
Product packers	0.11mg/ kgbw/day	LOAEL:	936	ii	negligible			ii				ii
(highest measured TWA-value)		103 mg/ kgbw/day						(ii)				
Typical concentration	0.056	103	1839	ii	negligible			ii				ii

								(ii)				
Short term (both RWC and typical)	negligible	103	-	ii	negligible			ii				ii
II. Formulation and processing												
Subscenario 1 Production of polycarbonate resins	0.002	103	51500	ii	negligible			ii				ii
RWC Short term	0.011	103	9363	ii	negligible			ii				ii
Subscenario 2 Production of phenolic resins	0.09	103	1144	ii	negligible			ii (ii)				ii
Subscenario 3 Production of epoxy resins (1 h/day)	0.94:8= 0.12	103	858	ii	6 (0.6)	103	17.2 (172)	**iii** (iii)	6.12 (0.72)	103	16.8 (143)	**iii** **(iii)**
III. End uses												
Subscenario 1 Use of polycarbonate	≤0.001			ii	negligible			ii (ii)			103000	ii (ii)
Subscenario 2 Use of phenolic resin Spray painting	1.7 0.34	103	60.6 303	iii iii	0.48 (0.048) 0.7 (0.07)	103	214 (2145) 147 (1471)	iii (ii) iii (ii)	2.18 (1.7) 1.04 (0.41)	103	47.2 (60.6) 99 (251)	iii (iii) iii (iii)
Subscenario 3 Use of epoxy resin Tank spraying, RWC	13.3 0.8	103	7.7 128.8	iii iii	7.3 (0.73) 51.4 5.14	103	14.1 (141) 2 (20)	iii (iii) iii (iii)	20.6 (14) 52.2 (5.9)	103	5 (7.4) 2 (17.5)	iii (iii) iii (iii)
Tank spraying, typical concentration	0.8	103	128.8	iii	14.6 (1.46)	103	7.1 (70)	iii (iii)	15.4 (2.26)	103	6.7 (45.6)	iii (iii)

Subscenario 4 Use of rubber additive	0.01	103	10 300	ii	0.002 (0.0002)	103	51 500 (515 000)	ii (ii)	0.012 (0.01)	103	8 583 (10 300)	ii (ii)

4.1.3.2.5 Mutagenicity

Based on the available data ptBP does not fulfil the criteria for classification as mutagenic. A conlusion ii is drawn for all scenarios.

4.1.3.2.6 Carcinogenicity

It is considered unlikely that ptBP should be a human carcinogen. However, its ability to increase the frequency of squamous cell carcinomas in the rat forestomach following initiation with MNNG indicates that ptBP may act as a tumour promoter in rats. The available studies on carcinogenicity are not sufficient to assess to carcinogenic potential of ptBP, but as ptBP most probably is not mutagenic; it is unlikely that the substance is carcinogenic. A conclusion ii is drawn for all scenarios.

4.1.3.2.7 Toxicity for reproduction

A NOAEL of 800 ppm corresponding to a NOAEL of 70 mg/kg bw/day was concluded from a 2-generation study in Sprague-Dawley rats (OECD Guideline 416 and US EPA Guideline OPPTS 870.3800, Clubb and Jardine, 2006) This value is used in the risk characterisation for reproduction, both fertility and developmental.

Effects on fertility

The calculated MOS values for fertility will be the same as those given for repeated dose toxicity in table 4.43 a). Also the same uncertainties factors will be used as for repeated dose toxicity and a min MOS =50.

A conclusion iii is drawn for

- II.3 Formulation and processing, Production of epoxy resins (dermal without PPE), (combined without PPE)
- III.2 End uses, Use of phenolic resins (inhalation) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins (inhalation) (dermal without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (RWC): (dermal, with and without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (typical conc): (dermal, with and without PPE) (combined, with and without PPE)

Developmental toxicity

The calculated MOS values for developmental toxicity will be the same as those given for repeated dose toxicity in table 4.43 a).

A minimal MOS is calculated from assessment factors based on default values given in the TGD draft from February 2005.

Interspecies: 10 (4(rat) x 2.5)

Intraspecies: 10 (there will be made no distinction between the progeny of the occupational population and the general population)

Differences in duration of exposure: 1 (2-generation study)

Route to route extrapolation: 1 (accounted for before the calculation of the MOS)

Dose-response relationship: 1 (the starting point for the MOS calculation is a NOAEL)

min MOS= 10x10=100

The min MOS value is compared with the MOS values given in table 4.43 a) for repeated dose toxicity. In addition to the scenarios in table 4.43 a) with concern and concl iii), the following scenarios with MOS in the range 50 – 100 will also give conclusion iii) for development:

- II.3 Formulation and processing, Production of epoxy resins (dermal without PPE), (combined with and without PPE)
- III.2 End uses, Use of phenolic resins (inhalation) (combined, with and without PPE)
- III.2 End uses, Use of phenolic resins, spray painting (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins (inhalation) (dermal with and without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (RWC): (inhalation) (dermal, with and without PPE) (combined, with and without PPE)
- III.3 End uses, Use of epoxy resins, tank spraying (typical conc): (inhalation) (dermal, with and without PPE) (combined, with and without PPE)

4.1.3.2.8 Summary of risk characterisation for workers

Summary of risk characterisation for workers is given in table 4.44 a) and b) below.

Table 4.44 a) Overview over the conclusions with respect to occupational risk characterisation (for RDT see table 4.44 b)

	Acute toxicity		Irritation			Sensitisation	Mutagenicity	Carcinogenicity
	Dermal	Inhalation	Dermal	Inhalation	Eye			
I. Production								
Product packers (highest measured value)	ii	ii	ii	ii	ii	ii	ii	ii
Typical concentration	ii	ii	ii	ii	ii	ii	ii	ii
II. Formulation and processing								
II.1 Production of polycarbonate resins	ii	ii	ii	ii	ii	ii	ii	ii
II.2 Production of phenolic resins	ii	ii	ii	ii	ii	ii	ii	ii
II.3 Production of epoxy resins	ii	ii	ii	ii	ii	ii	ii	ii
III. End Uses								
III.1 Use of polycarbonates	ii	ii	ii	ii	ii	ii	ii	ii
III.2 Use of phenolic resin	ii	ii	ii	ii	ii	ii	ii	ii
Spray painting	ii	ii	ii	ii	ii	ii	ii	ii
III.3 Use of epoxy resin	ii	ii	ii	ii	ii	ii	ii	ii
Tank spraying, RWC	ii	ii	ii	ii	ii	ii	ii	ii
Tank spraying, typical concentration	ii	ii	ii	ii	ii	ii	ii	ii
III.4 Use of rubber additive	ii	ii	ii	ii	ii	ii	ii	ii

Table 4.44 b) Overview over the conclusions with respect to occupational risk characterisation RDT

	Repeated dose toxicity, systemic (min MOS = 50)			Repeated dose toxicity, depigmentation (min MOS = 525)			Reproductive toxicity Fertility min MOS = 50[a]	Reproductive toxicity Development min MOS = 100[b]
	Inhalation	Dermal (with PPE)	Combined (with PPE)	Inhalation	Dermal (with PPE)	Combined (with PPE)		
I. Production								

Product packers (highest measured value		ii	ii	ii	ii	ii	ii		
Typical concentration		ii	ii	ii	ii	ii	ii		
Short term (RWC and typical)		ii	ii	ii	ii	ii	ii		
II. Formulation and processing									
II.1 Production of polycarbonate resins		ii	ii	ii	ii	ii	ii		
Short term exposure		ii	ii	ii	ii	ii	ii		
II.2 Production of phenolic resins		ii	ii	ii	ii	ii	ii		
II.3 Production of epoxy resins (1 h/d)		ii	iii (ii)	iii (ii)	ii	iii (iii)	iii (iii)		iii
III. End Uses									
III.1 Use of polycarbonates		ii	ii	ii	ii	ii	ii		
III.2 Use of phenolic resin (1 h/d)		iii	ii (ii)	iii (iii)	iii	iii (ii)	iii (iii)		
Spray painting		ii	ii	ii	iii	iii (ii)	iii (iii)		iii
III.3 Use of epoxy resin		iii	iii (ii)	iii (iii)	iii	iii (iii)	iii (iii)		iii
Tank spraying, RWC		ii	iii (iii)	iii (iii)	iii	iii (iii)	iii (iii)		iii
Tank spraying, typical concentration		ii	iii (iii)	iii (iii)	iii	iii (iii)	iii (iii)		iii
III.4 Use of rubber additive		ii	ii (ii)	ii (ii)	ii	ii	ii		

[a] These will be the same as for RDT in the left coloumns and are not repeated here
[b] These will be the same as for RDT in the left coloumns except for the ones listed separately, see the text

4.1.3.3 Consumers

For consumer exposure four main exposure scenarios have been identified. The four exposure scenarios with their respective exposure estimates are given below and will be used in the risk characterisation of ptBP for consumers. In the calculation of the internal exposure to ptBP for the four scenarios a 100 % absorption is assumed for oral, dermal and inhalation exposure (for further information see section 4.1.2.1 Toxicokinetics, metabolism and distribution).

Scenario Ii: *Exposure from direct consumer use of small amounts of adhesives (superglue) containing ptBP*

The dermal external dose in scenario Ii was calculated to be 0.051 µg/kg bw/day based on a calculated exposure of 0.00036 mg/kg bw/event.

Scenario Iii: *Exposure from direct consumer use of large amounts of adhesives (Universal glue) containing ptBP*

The dermal external dose in scenario Iii was calculated to be 0.0203 mg/kg bw/day based on a calculated exposure of 0.142 mg/kg bw/event.

Scenario II: *Exposure to ptBP in drinking water from drinking water reservoirs and pipelines*

The oral internal dose of ptBP in scenario II was calculated to be 0.0057 µg/ kg bw/day from drinking water reservoirs, and 0.027 µg/ kg bw/day from pipelines.

Scenario III: *Exposure to ptBP from polycarbonate used for food contact applications*

The internal oral dose of ptBP in scenario III was calculated to be 0.23 µg/ kg bw/day.

Scenario IV: *Exposure to ptBP from epoxy resins used for canned food*

The internal oral dose of ptBP in scenario IV was calculated to be 0.71 µg/ kg bw/day.

4.1.3.3.1 Acute toxicity

PtBP appears to have low acute toxicity by all three exposure routes. A limit test gives a LC_{50} for inhalation above 5600 mg/m^3 (dust aerosol) with an additional vapour component of 30 mg/m^3. Most studies show dermal and oral LD_{50} values above 2000 mg/kg bw.

Some hobbyists use adhesives containing ptBP and therefore a MOS and min MOS value is calculated. The applied LOAEL is based on the study by Sandoz Chemicals (1991) since there are no other suitable studies available for this endpoint. This study is performed as a limit dose test with only one dose level which gives an LD_{50} of > 2000 mg/kg bw/day. Consequently the estimated LOAEL is estimated to be 2000 mg/kg bw/day.

Acute toxicity, systemic:

Interspecies: 10 (4 (rat) x 2.5)
Intraspecies: 10 (standard for general population)
Difference in duration of exposure: 1 (acute dose toxicity study)
Dose-respons relationship: 3 (assessment factor for the use of LOAEL insted of a NOAEL)

Minimal MOS systemic acute toxicity: 300 = (10 x 10 x 1x3)

Scenario Ii, *Exposure from direct consumer use of small amounts of adhesives (superglue) containing ptBP*

Based on the exposure a LOAEL is estimated for acute toxicity (2000 mg/kg bw/day) the MOS for **systemic acute** toxicity is 5555600. Compared to the minimal MOS (300) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Scenario Iii, *Exposure from direct consumer use of large amounts of adhesives (Universal glue) containing ptBP*

Based on the exposure there is estimated a LOAEL for acute toxicity (2000 mg/kg bw/day) the MOS for **systemic acute** xicity is 14100. Compared to the minimal MOS (300) no concern is expected for consumers in this exposure scenario (Conclusion ii).

4.1.3.3.2 Irritation and corrosivity

Dermal

Scenario I, exposure from direct consumer use of adhesives containing ptBP

PtBP is regarded as irritating to skin following exposure to 500 mg ptBP under semi occluded conditions according to acceptable test guidelines. However, since the dermal exposure to ptBP during the use of adhesives containing up to 1% ptBP is very low, dermal exposure to products containing up to 1% ptBP will give no raise to concern (Conclusion ii).

Eye

Scenario I, exposure from direct consumer use of adhesives containing ptBP

PtBP has been shown to be irritating to the eyes. No scenario for eye exposure to ptBP has been performed; however exposure to eyes may occur during the use of adhesives. However, since the residual amount of ptBP in adhesives is low, up to 1%, eye exposure to products containing up to 1% ptBP will give no raise to concern (Conclusion ii).

4.1.3.3.3 Corrosivity

In the evaluation of the data on irritating/corrosive effects, ptBP is not considered to be corrosive to skin (Conclusion ii).

4.1.3.3.4 Sensitisation

The database for assessing skin sensitisation for ptBP has limitations. The human studies have major limitations in both number of test samples and mainly that the patients were suffering from former skin allergy or other skin diseases. Although the animal data are of varying reliability the conclusion is drawn that ptBP does not fulfill the classification criteria as a sensitizer. (Conclusion ii)

4.1.3.3.5 Repeated dose toxicity

A NOAEL of 70 mg/kg bw/day was concluded from a 2-generation reproduction toxicity study in Sprague-Dawley rats (Clubb and Jardine, 2006). This value is used in the risk characterisation both for repeated dose toxicity and reproductive toxicity (effects on fertility and development).

The systemic LOAEL for mice (103 mg/kgbw/day) found by Hara et al., 1969 is used in the assessment of depigmentation as an endpoint.

There is no need for correction for differences in bioavailability between the different routes (as determined by the percentages of absorption) as the absorption is estimated to be 100 % via oral as well as skin uptake.

Minimal MOS-values are calculated from assessment factors based on default values given in the TGD draft from February 2005:

Repeated dose toxicity, systemic:

Interspecies: 10 (4 (rat) x 2.5)
Intraspecies: 10 (standard for general population)
Difference in duration of exposure: 1 (2 generation study)

Minimal MOS systemic repeated dose toxicity: 100 = (10 x 10 x 1)

Repeated dose toxicity, depigmentation:

Interspecies: 17.5 (7 (mice) x 2.5)
Intraspecies: 10 (standard for general population9
Difference in duration of exposure: 2 (oral exposure leading to systemic depigmentation in mice 1 single injection of one single dose)
Dose-respons relationship: 3 (assessment factor for the use of LOAEL insted of a NOAEL)

Minimal MOS systemic depigmentation: 1050 = (17.5 x 10 x 2 x 3)

The minimal MOS values are compared to the MOS values. This will give a conclusion ii for all scenarios.

Scenario Ii, *Exposure from direct consumer use of small amounts of adhesives (superglue) containing ptBP*

Based on the exposure and the NOAEL for repeated dose toxicity (70 mg/kg bw/day) the MOS for repeated dose toxicity is 1370000. Compared to the minimal MOS (100) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Based on the exposure and the LOAEL for depigmentation (103 mg/kg bw/day) the MOS for depigmentation is 2019608. Compared to the minimal MOS (1050) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Scenario Iii, *Exposure from direct consumer use of large amounts of adhesives (Universal glue) containing ptBP*

Based on the exposure and the NOAEL for repeated dose toxicity (70 mg/kg bw/day) the MOS for repeated dose toxicity is 3500. Compared to the minimal MOS (100) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Based on the exposure and the LOAEL for depigmentation (103 mg/kg bw/day) the MOS for depigmentation is 5150. Compared to the minimal MOS (1050) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Scenario IIa, *Exposure to ptBP in drinking water from drinking water reservoirs*

Based on the exposure and the NOAEL for repeated dose toxicity (70 mg/kg bw/day) the MOS for repeated dose toxicity is 12300000. Compared to the minimal MOS (100) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Based on the exposure and the LOAEL for depigmentation (103 mg/kg bw/day) the MOS for depigmentation is 18070200. Compared to the minimal MOS (1050) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Scenario IIb, *Exposure to ptBP in drinking water from pipelines*

Based on the exposure and the NOAEL for repeated dose toxicity (70 mg/kg bw/day) the MOS for repeated dose toxicity is 2600000. Compared to the minimal MOS (100) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Based on the exposure and the LOAEL for depigmentation (103 mg/kg bw/day) the MOS for depigmentation is 3820000. Compared to the minimal MOS (1050) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Scenario III, *Exposure to ptBP from Polycarbonate used for food contact applications*

Based on the exposure and the NOAEL for repeated dose toxicity (70 mg/kg bw/day) the MOS for repeated dose toxicity is 300000. Compared to the minimal MOS (100) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Based on the exposure and the LOAEL for depigmentation (103 mg/kg bw/day) the MOS for depigmentation is 448000. Compared to the minimal MOS (1050) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Scenario IV, *Exposure to ptBP from Epoxy resins used for canned food.*

Based on the exposure and the NOAEL for repeated dose toxicity (70 mg/kg bw/day) the MOS for repeated dose toxicity is 99000. Compared to the minimal MOS (100) no concern is expected for consumers in this exposure scenario (Conclusion ii).

Based on the exposure and the LOAEL for depigmentation (103 mg/kg bw/day) the MOS for depigmentation is 145000. Compared to the minimal MOS (1050) no concern is expected for consumers in this exposure scenario (Conclusion ii).

4.1.3.3.6 Mutagenicity

Based on the available data ptBP does not fulfil the criteria for classification as mutagenic. A conlusion ii is drawn for all scenarios.

4.1.3.3.7 Carcinogenicity

It is considered unlikely that ptBP should be a human carcinogen. However, its ability to increase the frequency of squamous cell carcinomas in the rat forestomach following initiation with MNNG indicates that ptBP may act as a tumour promoter in rats. The available studies on carcinogenicity are not sufficient to assess to carcinogenic potential of ptBP, but as ptBP most probably is not mutagenic; it is unlikely that the substance is carcinogenic. A conclusion ii is drawn for all scenarios.

4.1.3.3.8 Toxicity for reproduction

The risk characterisation of reproductive toxicity is similar to the risk characterisation of repeated dose toxicity based on the NOAEL of 70 mg/kg bw/day, see paragraph 4.1.3.3.5.

4.1.3.3.9 Summary of risk characterisation for consumers

A summary of risk characterisation for consumers is given in table 4.45. a) and b) in addition to table 4.46 below. From the calculation of MOS-values and the comparison to the minimal MOS values there are no concern for the exposure to ptBP for consumers (Conclusion ii).

Table 4.45a MOS values for the four consumer scenarios

Scenarios/Endpoint	scenario Ii	scenario Iii	scenario II	scenario III	scenario IV
Acute toxicity	5555600	14100			
Repeated dose	1370 000	3500	12300000[a]	300 000	99 000

toxicity (RDT)			2600 000[b]		
Depigmentation	2019608	5150	18070200[a] 3820000[b]	448000	145000
Reproductive toxicity	1370 000	3500	12300000[a] 2600 000[b]	300 0000	99 000

[a]Exposure to ptBP in drinking water from drinking water reservoirs

[b]Exposure to ptBP in drinking water from pipelines

Table 4.45b Minimal MOS values for the four consumer scenarios

Scenarios/Endpoint	scenario Ii	scenario Iii	scenario II	scenario III	scenario IV
Acute toxicity	300	300			
Repeated dose toxicity (RTD)	100	100	100[a] 100[b]	100	100
Depigmentation	1050	1050	1050[a] 1050[b]	1050	1050
Reproductive toxicity	100	100	100[a] 100[b]	100	100

[a]Exposure to ptBP in drinking water from drinking water reservoirs

[b]Exposure to ptBP in drinking water from pipelines

Table 4.46 Conclusions for the four consumer exposure scenarios

Endpoint	Conclusion scenario I	Conclusion scenario II	Conclusion scenario III	Conclusion scenario IV
Acute toxicity	ii/ii (scenario Ii/ scenario Iii)	ii	ii	ii
Irritation/corrosivity skin	ii			
Irritation eye	ii			
Corrosivity	ii			

Sensitisation	ii			
Repeated dose toxicity	ii/ii (scenario Ii/ scenario Iii)	ii	ii	ii
Depigmentation	ii/ ii (scenario Ii/ scenario Iii)	ii	ii	ii
Mutagenicity	ii	ii	ii	ii
Carcinogenicity	ii	ii	ii	ii
Reproductive toxicity	ii/ ii (scenario Ii/ scenario Iii)	ii	ii	ii

4.1.3.4 Humans exposed via the environment.

The endpoints associated with exposure to ptBP are repeated dose toxicity, mutagenicity, carcinogenicity and reproductive toxicity including both effects on fertility and developmental effects in offspring. These effects are considered in the risk characterisation of indirectly exposure via the environment, and for combined exposure to ptBP.

According to the scenarios described in the environmental section 3.1.1 the human intake of ptBP from air, drinking water, fish, leaf crops, root crops, meat and milk for production site B, and from local scenarios from production of phenolic resins and epoxy resins, as well as the regional exposure scenario as estimated by EUSES are shown in table 4.47 .

Table 4.47 Estimated human intake of ptBP in mg/kg bw/day from air, drinking water, fish, leaf crops, root crops, meat and milk for local site specific scenarios and local and regional scenarios as estimated by EUSES (TGD).

Scenarios[a]	**Drinking water**	**Air**	**Fish**	**Leaf crops**	**Root crops**	**Meat**	**Milk**	**Total**
Production site B	**$1.7x10^{-4}$**	**$6.1x10^{-5}$**	**$2.2x10^{-5}$**	**$1.4x10^{-3}$**	**$6.5x10^{-4}$**	**$1.2x10^{-6}$**	**$7.2x10^{-7}$**	**$2.3x10^{-3}$**
Production of polycarbonates								
Site A	-	-	-	-	-	-	-	-
Site B	-	-	-	-	-	-	-	-
Site C	-	-	-	-	-	-	-	-
Production of phenolic resins								
Site specific	-	-	-	-	-	-	-	-
Generic, TGD calculation	**$4.2x10^{-3}$**	**$3.5x10^{-6}$**	**0.029**	**$3.7x10^{-4}$**	**$7x10^{-3}$**	**$1.9x10^{-6}$**	**$1.1x10^{-6}$**	**0.0403**
Production of epoxy resins								
Sub-scenario 1 TGD calculation	**$8x10^{-3}$**	**$1x10^{-6}$**	**0.033**	**$1.3x10^{-3}$**	**0.031**	**$3.8x10^{-6}$**	**$2.2x10^{-6}$**	**0.073**
Sub-scenario	**$2.9x10^{-5}$**	**$1.6x10^{-3}$**	**$6x10^{-5}$**	**0.036**	**$1.1x10^{-4}$**	**$3x10^{-5}$**	**$1.8x10^{-5}$**	**0.038**

2+3 TGD calculation								
Sub-scenario 4 TGD calculation	**$2x10^{-3}$**	**$3.6x10^{-7}$**	**$6.3x10^{-3}$**	**$3.2x10^{-4}$**	**$7.7x10^{-3}$**	**$9.5x10^{-7}$**	**$5.6x10^{-7}$**	**0.016**
Regional	**$2.7x10^{-6}$**	**$2.2x10^{-7}$**	**$1.9x10^{-5}$**	**$4.8x10^{-6}$**	**$4.7x10^{-7}$**	**$5.1x10^{-9}$**	**$3x10^{-9}$**	**$2.7x10^{-5}$**

[a]Referes to scenarios described in section 3.1.1.

The daily human intake via the environment based upon typical human consumption and inhalation rates at the regional level is 2.7 x 10^{-5} mg/kg bw/day, and the highest local exposure scenario (epoxy resin production) is 0.073 mg/kg bw/day.

The daily human regional exposure level and the highest local exposure level as estimated by EUSES and their corresponding MOS values for effects of ptBP (repeated dose toxicity, fertility and developmental effects in offspring) are indicated in table 4.48.

The Minimal MOS values are compared to the MOS values below. This will give a conclusion ii for all scenarios.

Table 4.48 MOS values for indirect human regional and local exposure to ptBP via the environment

Scenario[a]	**Human intake mg/kg bw/day**	**MOS repeated dose toxicity[b]**	**MOS RDT, depigmentation[c]**	**MOS fertility/development[b]**
Regional exposure	2.7 x 10^{-5}	2600 000	3800000	2600 000
Local exposure	0.073	960	1400	960

[a]Referes to the scenarios described in section 3.1.1

[b]NOAELvalue (70 mg/kg/day) from an oral 2-generation reproduction toxicity study in rats (Clubb and Jardine, 2006).

[c] LOAEL (103 mg/kg/day) value from an oral exposure depigmentation study in mice (Hara and Nakajima, 1969).

The MOS values for repeated dose toxicity and fertility/development at 2600 000 for indirectly regional exposure to ptBP and the MOS value of 960 for indirectly local exposure to ptBP are considered sufficient compared to the min MOS-value of 100, indicating no concern for exposure to ptBP from regional and local exposure scenarios (Conclusion ii).

The MOS values for repeated dose toxicity - depigmentation at 3800000 for indirectly regional exposure to ptBP and the MOS value of 1400 for indirectly local exposure to ptBP are considered sufficient compared to the min MOS-value of 1050, indicating no concern for exposure to ptBP from regional and local exposure scenarios (Conclusion ii).

Based on the available data ptBP does not fulfil the criteria for classification as mutagenic. A conlusion ii is drawn for all scenarios.

It is considered unlikely that ptBP should be a human carcinogen. However, its ability to increase the frequency of squamous cell carcinomas in the rat forestomach following initiation with MNNG indicates that ptBP may act as a tumour promoter in rats. The available studies on carcinogenicity are not sufficient to assess to carcinogenic potential of ptBP, but as ptBP most probably is not mutagenic; it is unlikely that the substance is carcinogenic. A conclusion ii is drawn for all scenarios.

Table 4.49 Summary of the conclusions for humans exposed via the environment

Critical endpoint	Local exposure[a]	Regional exposure[b]
Repeated dose toxicity	ii	ii
RDT, depigmentation	ii	ii
Mutagenicity	ii	ii
Carcinogenicity	ii	ii
Reproductive toxicity	ii	ii

[a]Highest indirect local exposure (production of epoxy resins) as estimated by EUSES (0.073).

[b]Indirect regional exposure as estimated by EUSES

4.1.3.5 Combined exposure

Humans may be exposed to ptBP via direct use of products with phenolic resins or epoxy resins containing residual ptBP monomers, or via the use of the final product containing residual concentrations of ptBP. Human exposure is possible via intake of food stored in products made of polycarbonates such as containers for storage of food and tableware or from canned food. The combined exposure to ptBP is the sum of all the specific sources (occupational exposure, consumer exposure, and indirectly exposure via the environment), and by all routes of exposure (oral, dermal and inhalation). However, since occupational exposure values will totally dominate the exposure levels (workers: Inhalation exposure (internal) at production: epoxy resins 0.94 mg/kg/day; phenolic resins 0.09 mg/kg/day, During end use: epoxy resins 13.3 mg/kg/day; Phenolic resins 1.7 mg/kg/day), it is not considered relevant to make a separate calculation for combined exposure including occupational exposure. If we included the exposure levels from the work exposure the MOS for repeated dose toxicity and fertility would have been clonclusion iii (as it already is concluded in table 4.44 b) for workers).

The effects of ptBP considered are repeated dose toxicity, mutagenicity, carcinogenicity and reproductive toxicity including both effects on fertility and developmental effects in offspring. In table 4.50 the combined exposure to ptBP with their corresponding MOS values for repeated dose toxicity, fertility and developmental effects in offspring are presented (minus occupational exposure). Since no threshold level N(L)OAEL has been identified for skin irritation or sensitisation, no MOS values have been derived for these endpoints.

Table 4.50 MOS values for combined exposure to ptBP

Scenario	Daily intake mg/kg bw/day	MOS Repeated dose toxicity[a]	MOS RDT, depigmentation[b]	MOS fertility/development[a]
Ii Adhesives containing ptBP, super glue	0.000051			
Iii Adhesives containing ptBP, universal glue	0.0203			
II Drinking water reservoirs and pipelines	0.000033			
III Polycarbonate used for food contact applications	0.00023			
IV Epoxy resins used for canned food	0.00071			
Local exposure[c]	0.073			
Regional exposure	0.000027			
Combined local[c]	**0.074[d] / 0.094[d]**	**950 [d] / 750[e]**	**1390[d] / 1100[e]**	**950 [d] /750[e]**
Combined regional	**0.0011 [d] / 0.0211[e]**	**64 000[d] / 3320[e]**	**93640[d]/ 4880[e]**	**64 000 [d] /3320[e]**

[a]NOAEL value from an oral 2-generation reproduction toxicity study in rats (Clubb and Jardine, 2006).
[b] LOAEL (103 mg/kg/day) value from an oral exposure depigmentation study in mice (Hara and Nakajima, 1969).
[c]Highest exposure scenario for local exposure (epoxy resin production)
[d] Included scenario Ii.
e Included scenario Iii

The MOS values for repeated dose toxicity, fertility and developmental effects in offspring for the highest combined local exposure scenario are considered sufficient compared to the min MOS-value of 100, indicating no concern for combined local exposure to ptBP (Conclusion ii).

The MOS values for repeated dose toxicity, depigmentation for the combined regional exposure scenario are considered sufficient compared to the min MOS-value of 1050, indicating no concern for combined regional exposure to ptBP (Conclusion ii).

Based on the available data ptBP does not fulfil the criteria for classification as mutagenic. A conlusion ii is drawn for all scenarios.

As regards the carcinogenic potential of ptBP an increase in the frequency of squamous cell carcinomas in the rat forestomach following initiation with MNNG was reported indicating that ptBP may have a tumor promoter effect in rats. However, the doses of ptBP inducing forestomach tumors in animals (600 – 1230 mg/kg) is much higher than the highest local combined exposure to ptBP (0.074 mg/kg bw/day) and the combined regional exposure to ptBP (0.0011 mg/kg bw/day), indicating no concern for exposure to ptBP regarding carcinogenicity following combined human local or regional exposure to ptBP. The available

studies on carcinogenicity are not sufficient to assess to carcinogenic potential of ptBP, but as ptBP most probable is not mutagenic; it is unlikely that the substance is carcinogenic. (Conclusion ii).

Table 4.51 Summary of the conclusions for combined exposure to ptBP

Critical endpoint	Combined local exposure	Combined regional exposure
Repeated dose toxicity	ii	ii
RDT, depigmentation	ii	ii
Mutagenicity	ii	ii
Carcinogenicity	ii	ii
Reproductive toxicity	ii	ii

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

PtBP has low (0.5 Pa at 20°C) vapour pressure. No data is available for flammability. The substance is combustible (Lewis Sr., 2007). The flash point is about 115°C. The chemical structure of this compound does not suggest a likelihood of explosivity or oxidizing properties. The risks from physicochemical properties are of no concern to either subpopulation (workers, consumers or humans exposed via the environment). Conclusion ii) is reached.

5 RESULTS [10]

5.1 ENVIRONMENT

Conclusion (i) There is a need for further information and/or testing.

Conclusion (i) applies to endocrine disruption. Based on *in vitro* data on ptBP and read across from similar alkyl phenol compounds, including p-tert-pentylphenol, which have shown endocrine disrupting properties *in vivo*, it is concluded that further testing should be required for ptBP. As a "Tier 2 test" an Extended Early Life-Stage test on fish according to the draft OECD guideline will be performed.

Conclusion (i) applies to phenolic resin production site 5, where the PEC_{marine} as well as the PEC_{STP} have been calculated using generic parameters and a risk to the marine environment and to microorganisms in the WWTP has been identified. The exact values for the PEC/PNEC ratios are not given as the tonnage used at this site is considered confidential. Further exposure information is needed in order to refine the the PEC_{marine} and the PEC_{STP} for this site.

Conclusion (i) applies to phenolic resin production site 6 where no site specific data is available. No $PEC_{aquatic}$ and no PEC_{STP} could be derived and therefore no risk assessment for the aquatic compartment and for microorganisms in the WWTP has been carried out. Further exposure information is needed in order to calculate a $PEC_{aquatic}$ and a PEC_{STP} for this site.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to the life-cycle steps production, to the production of phenolic resins, where site specific data are available, for the generic sub-scenario 2 and 3 of the production of epoxy resins and to the production of polycarbonate resins for all environmental compartments.

Conclusion (ii) applies to phenolic resin production site 8 for the marine environment. The PEC/PNEC ratio for the marine environment is below 0.03.

According to information from industry no emissions to the environment are expected from the use of ptBP in the production of oilfield chemicals and the scenario "Hydrogenation" and therefore conclusion (ii) applies.

[10] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

No risk assessment for secondary poisoning has been performed. Available data indicate that ptBP is unlikely to bioaccumulatein the food chain. No further information is considered necessary.

Conclusions ii) for the aquatic and the terrestrial compartment have to be seen as provisional until possible endocrine effects in fish have been resolved.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the generic scenario for phenolic resin production and to the generic sub-scenarios 1 and 4 of the epoxy resin production for the aquatic compartment (including sediment). The PEC/PNEC ratios for phenolic resin production and for sub-scenarios 1 and 4 of the epoxy resin production are 28, 121 and 30, respectively.

Conclusion (iii) also applies to the generic scenario for phenolic resin production and to the generic sub-scenarios 1 and 4 of the epoxy resin production for the terrestrial compartment (PEC/PNEC ratios 15, 66 and 17, respectively) and for microorganisms in WWTPs (PEC/PNEC ratios 1.2, 5.2 and 1.3, respectively).

For production of phenolic resins site specific information has been obtained only for about 50 % of the total tonnage used in this use category. Therefore a generic scenario has been conducted which resulted in a risk to the aquatic and the terrestrial compartment, as well as to microorganisms in WWTPs. The exposure assessment for the production of phenolic resins is based on an average emission factor obtained from the site having the highest emissions participating in the EPRA water monitoring program and on default parameters from the TGD. The size of the site has been chosen in close cooperation with industry.

Concerning the production of epoxy resins no site specific data has been obtained by industry but only qualitative descriptions of the processes involved. No site-specific data on emissions to the environment has been obtained. The information received resulted in four sub-scenarios, which have been proposed by industry. TGD default parameters have been used to calculate environmental concentrations. The TGD values have partly been adapted due to information from industry (sub-scenario 4).

Regarding the release from ambient cured epoxy products no further information on releases to the environment has become available.

More site specific information may give evidence of lower emissions than estimated in the generic scenarios of the use categories “phenolic resins” and “epoxy resins”, maybe resulting in no risk. However, no such data could be made available despite of much effort that has been undertaken by the ptBP producers to obtain this information during the last 1 ½ years.

5.2 HUMAN HEALTH:

5.2.1 Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to the endpoints acute toxicity, irritation, sensitisation, mutagenicity and carcinogenicity for all scenarios.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to the endpoints of repeated dose toxicity and reproductive toxicity after dermal exposure arising from formulation and processing (production of epoxy resins) and after inhalation and dermal exposure arising from end use of phenolic resins and end use of epoxy resins. Conclusion (ii) is reached for all other endpoints and scenarios.

5.2.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios and endpoints for consumers.

5.2.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios and endpoints for humans exposed via the environment.

5.2.4 Combined exposure

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios and endpoints for combined exposure. Combined expsure is described as exposure to humans as consumers and via the environment. For humans exposed both in the working environment as well as consumers or indirect via the environment, the occupational exposure will exceed the other exposure sources by far, so it has not been considered relevant to assess combined exposure including workers.

5.3 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

PtBP has low vapour pressure. No data is available for flammability. The substance is reported to be combustible. The flash point is about 115°C. The chemical structure of this compound does not suggest a likelihood of explosivity or oxidizing properties. The risks from physicochemical properties are of no concern to either subpopulation (workers, consumers or humans exposed via the environment).

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios

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7 ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests

EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient

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Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
pKa	negative log of the acid dissociation constant
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
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
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document [1]
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material

vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

8 APPENDIX

Appendix A:

Personal protective equipment[9]

Production of ptBP-use of PPE

Type of operation	Hand Protection	Eye Protection	Skin Protection	Respiratory protection
Filling in tank containers/ tank cars	Safety gloves		Disposable protective coverall (Kleenguard $T5_6$)	Dust mask while docking/Filter mask with combination filter while undocking
Repairs of process equipment in contact with ptBP	Safety gloves		Disposable protective coverall (Kleenguard $T5_6$))	Dust mask if solid product or filter mask with combination filter if melt
Product recycling	Safety gloves		Disposable protective coverall (Kleenguard $T5_6$)	Dust mask if recycling via sluice, filter mask with combination filter if recycling via melt container
Packing	Safety gloves	Basket protective spectacles or protective spectacles and visor	Disposable protective coverall (Kleenguard $T5_6$)	Dust mask if solid product or filter mask with combination filter if melt
Laboratory operations/sampling	Safety gloves	Basket protective spectacles	Chemical resistant apron or disposable protective coverall (Kleenguard $T5_6$)	Dust mask

Industry is asked to provide more information about the material in the safety gloves and type of dust masks.

Production of polycarbonates – use of PPE [9]

Company A

Type of operation	On a weekly or monthly basis	Hand Protection	Eye Protection	Skin Protection	Respiratory protection
Unloading of ptBP	yes	Neoprene gloves	Visor of full face piece	Chemical protective suit	Positive air purifying

			incorporated in respirator	(film laminate on polypropylene substrate)	respirator
Maintenance of process equipment in contact with ptBP	No	Neoprene gloves	Visor of full face piece incorporated in respirator	Chemical protective suit (film laminate on polypropylene substrate)	Positive air purifying respirator
Laboratory operations	Yes	Latex gloves	Safety goggles (polycarbonate)	Body covering clothing	None: Performed in fume cupboard
Disposal/waste management of ptBP	No	Neoprene gloves	Visor of full face piece incorporated in respirator	Chemical protective suit (film laminate on polypropylene substrate)	Positive air purifying respirator

Company B, Site A

Type of operation	On a weekly or monthly basis	Hand Protection	Eye Protection	Skin Protection	Respiratory protection
Unloading of ptBP	No	PVC gauntlets	Visor of full face piece incorporated in respirator	Chemical protective suit (PVC)	Full face gas mask with ABEK filter cartridge
Maintenance of process equipment in contact with ptBP	No	PVC gauntlets	Visor of full face piece incorporated in respirator	Chemical protective suit (PVC)	Full face gas mask with ABEK filter cartridge
Laboratory operations	No	PVC gloves	Safety goggles (polycarbonate)	Body covering clothing (polyester cotton)	None: Operation performed in fume cupboard
Disposal/waste management of ptBP	No	PVC gauntlets	Depending on the task: Face shield (polycarbonate) or Visor of full face piece incorporated in respirator	Chemical protective suit (PVC)	Depending on task: none or Full face gas mask with ABEK filter cartridge
Sampling of molten ptBP	No	PVC gauntlets	Visor of full face piece incorporated in respirator	Chemical protective suit (PVC)	Full face gas mask with ABEK filter cartridge

Company B, Site B

Type of operation	On a weekly or monthly basis	Hand Protection	Eye Protection	Skin Protection	Respiratory protection
Unloading of ptBP	Yes	Thick stuffed leather gloves	Visor of full face piece incorporated in respirator	Chemical protective suit (polypropylene)	Full face gas mask with ABEK filter cartridge
Disposal/waste management of ptBP	No	PVC gloves	Depending on task: Safety goggles (polycarbonate) or Visor of full face piece incorporated in respirator	Chemical protective suit (polypropylene)	Depending on task: none or full face gas mask with ABEK filter cartridge
Maintenance of process equipment in contact with ptBP	No	PVC gloves	Visor of full face piece incorporated in respirator	Chemical protective suit (polypropylene)	Full face gas mask with ABEK filter cartridge
Laboratory operations	No	Rubber gloves	Safety goggles (polycarbonate)	Body covering clothing (rubber apron)	None: operation performed in fume cupboard

Appendix B

Sampling procedures

Ref number	Personal/ Area	Sampler	Flow rate	Sampling time	Analytical Method	Detection limit
1	Personal	Tenax		8 hours	Thermodesorption gas chromatography	1 μg
2	Personal	-	-	30 seconds	-	-
3	Personal	Ambulant system	-	8 hours	Gas chromatography	-
4	Area	-	-	4 hours	Gas chromatography	0.02 mg/m^3
5	Biological	Urine			Gas liquid chromatography	0.2 μg/ml
6	Personal	Micro impinger	1.2-2 l/min	2-5 samples taken during a 12 hour shift	Gas chromatography	0.2 μg/ml
8 A*	Personal and area	Silicagel	-	-	High performance liquid chromatography	0.2 $\mu g/m^3$
8 B*		Tenax	1 l/min		Gas chromatography Mass spectroscopy	0.05 ppm
9		Silicagel	200 ml/min		High performance liquid chromatography	0.2 μg
10		Tenax	-	-	Gas chromatography	0.03 mg/m^3
12	Biological	Urine			-	-
20	Area	Tenax	10 L in 3 hours		Gas chromatography	0.03 mg/m^3
19	Personal/stationary	Silica tubes	5L/min Stationary 2L/min Personal	1-2.4 hours	High performance l liquid chromatography	nd<0.01 mg/m^3

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The report provides the comprehensive risk assessment of the substance p-tert-butylphenol It has been prepared by Norway in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The environmental risk assessment concludes that there is concern for the aquatic and terrestrial compartments and the functioning of waste water treatment plants for certain processing scenarios (phenolic resin and epoxy resin production). For production and other uses of the substance further information is needed before definitive conclusions can be drawn with respect to the risks for the freshwater, marine and terrestrial compartments and the functioning of waste water treatment plants. Information is needed on the endocrine effects of the substance. There is no concern for the atmosphere and secondary poisoning via the food chain.

For human health, there is concern for workers, in terms of repeated dose toxicity and reproductive toxicity, but neither for consumers, nor for humans exposed via the environment.