European Union Risk Assessment Report

4-TERT-BUTYLBENZOIC ACID

CAS No: 98-73-7

EINECS No: 202-696-3

RISK ASSESSMENT

July 2009

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

30.05.2008

Germany

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Date of Last Literature Search :	**2003**
Review of report by MS Technical Experts finalised:	**[insert month and year]**
Final report:	**[year]**

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: 98-73-7
EINECS Number: 202-696-3
IUPAC Name: 4-tert.-Butylbenzoic acid

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 for the intermediate processing site and use as resin modifier due to negligible emissions. The conclusion covers also the life-cycle stages of the use as stabiliser in PVC (manufacture of liquid mixed metal stabilisers, compounding and conversion, service life and disposal) due to zero or low exposure. All the scenarios mentioned do not cause risks for the compartments water, sediment, waste water treatment plants, air and soil. In addition, conclusion (ii) applies to the marine environment due to low exposure and as the substance does not meet the PBT-criteria.

Bioaccumulation in the aquatic and terrestrial food chain is expected to be negligible. Consequently, no assessment of secondary poisoning was conducted.

Human health

Human health (toxicity)

Workers

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

Conclusion (i) applies to mutagenicity. For adequate assessment of the genotoxic potential of 4-tert-butylbenzoic acid preferably a combination of an *in vivo* COMET assay (directly exposed tissue and liver) and a bone marrow micronucleus test is recommended.

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

Conclusion (i on hold) applies to developmental toxicity. Risk assessment with respect to developmental toxicity is not possible since there are no human or experimental data available. Conclusion (i on hold) is expressed keeping in mind that due to the low critical exposure level for systemic effects after repeated exposure (≈ 0.07 mg/m^3) risk reduction measures will be implemented, which could also cover risks regarding developmental toxicity.

[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.

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

Two occupational exposure scenarios have been identified: (1) production and further processing of PTBBA (2) Production of alkyd resins in the polymers industry.

For PTBBA, concern is expressed for systemic toxicity after acute and repeated contact and fertility effects, where systemic toxicity after repeated contact is the most relevant toxicological endpoint.

With respect to effects in the airways after repeated exposure, inhalation exposure levels of 4-tert-butylbenzoic acid should be controlled to values in the range of 0.067 mg/m^3 (critical exposure level of systemic effects after repeated exposure). In doing so, inhalation risks from other endpoints, especially risks of adverse fertility effects, as well as possible risks by developmental toxicity are similarly and effectively be mitigated too.

Special attention should be given to skin contact. From the risk assessment there is indication that repeated dermal exposure at the workplace to 4-tert-butylbenzoic acid may not exceed a daily exposure of 0.017 mg/kg/day or 1.2 mg/person/day. In doing so, dermal risks from other endpoints especially risks of adverse fertility effects and possible risks of developmental toxicity, as well as risks by acute toxicity are similarly and effectively be mitigated too.

Consumers

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

Conclusion (i on hold) applies to mutagenicity and developmetal toxicity. The C&L meeting in September 2007 decided for the substance repr. Cat2, R60. It is expected that the initiated risk reduction measures will also protect consumers for mutagenic as well for developmental toxic effects. Therefore, further testing is on hold for both toxicological endpoints in the light of the risk reduction strategy (conclusion i).

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 other toxicological endpoints except mutagenicity and developmental toxcicity.

Humans exposed via the environment

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

Conclusion (i on hold) applies to mutagenicity and developmental toxicity. The C&L meeting in September 2007 decided for the substance repr. Cat2, R60. It is expected that the initiated risk reduction measures will also protect for mutagenic as well for developmental toxic

effects. Therefore, further testing is on hold for both toxicological endpoints in the light of the risk reduction strategy (conclusion i).

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 repeated dose toxicity carcinogenicity and male fertility.

Human health (physico-chemical properties)

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.

CONTENTS

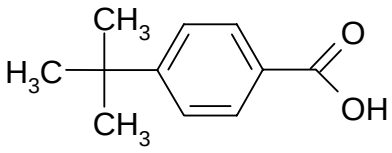
EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 98-73-7
EINECS Number: 202-696-3
IUPAC Name: 4-tert.-Butylbenzoic acid
Molecular formula: $C_{11}H_{14}O_2$
Structural formula:



Molecular weight: 178.23 g/mol

Synonyms: para-tert.-Butylbenzoic acid
PTBBA
4-(1,1-Dimethylethyl)benzoic acid

CAS Index Name: Benzoic acid, 4-(1,1-dimethylethyl)-

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: > 99 %

Impurities: therephthalic acid (CAS no. 100-21-0): < 1 %
4-acetylbenzoic acid (CAS no. 586-89-0): < 1 %
4-toluic acid (CAS no. 99-94-5): < 1 %
4-tert. butylbenzaldehyde (CAS no. 939-97-9): < 1 %

Additives: none

1.3 PHYSICO-CHEMICAL PROPERTIES

4-tert.-Butylbenzoic acid (PTBBA) is a white crystalline powder (at room temperature and normal pressure). Data on the physical and chemical properties are given in Table 1.1.

Table 1.1 Summary of physico-chemical properties

Property	Value	
Physical state	solid	
Melting point	165 - 167 °C [1)]	Fuso, 2003
Boiling point	280 °C (decomposition)	Merck, 2003
Relative density	1.142 at 20 °C	Lewis, 1993
Vapour pressure	0.057 Pa at 20 °C [2)]	Colomina, 1979
Water solubility	47.1 mg/l at 20 °C (pH 4.3) 12600 mg/l at 20 °C (pH 7); [3)]	Clariant France, 2003
Partition coefficient n-octanol/water (log value)	LogPow 3.4 at 21 °C [4)]	Hoechst, 1993
Acid-base dissociation constant	PKa 4.36 at 25 °C	Ludwig et al., 1986
Granulometry		
Conversion factors		
Flash point	not conducted (solid)	
Autoflammability	no selfignition up to the melting point	BAM, 2003
Flammability	non flammable according to A.10	Clariant, 2003
Explosive properties	no explosive properties (structural reasons)	BASF, 2000
Oxidizing properties	no oxidizing properties (structural reasons)	BASF, 2000
Viscosity		
Henry's constant	0.216 Pa m-3 mol-1	calculated
Surface tension	not conducted [5)]	

[1)] Capillary method

[2)] Colomina et al. have measured the vapour pressure of PTBBA at temperatures from 52 to 70 °C resulting in values from 0.062 to 0.43 Pa. When applying the Clausius-Claperyron equation the vapour pressure at 20 °C can be calculated to 0.057 Pa.

[3)] The water solubility is very much dependent on pH. PTBBA dissociates in the environmentally relevant pH range. The water solubility was consequently estimated by Wskowwin v1.41 and gave 12600 mg/l at 20 °C. Thus PTBBA is at pH 7 readily soluble in water.

[4)] HPLC method. The partition coefficient was also calculated according to Leo & Hansch and resulted in a $\log P_{ow}$ of 3.86. For the risk assessment, the experimental value is preferred.

[5)] Although PTBBA has a polaric carboxylic group the tert.-butyl benzene moiety is not apolar enough to expect a considerable reduction of the surface tension of aqueous solutions. Therefore no test was conducted.

1.4 CLASSIFICATION

1.4.1 Current classification

PTBBA is not included in Annex I of the Directive 67/548/EEC. Industry has voluntarily used classification R51/53 for the environment and R20/21/22/48/62 for the human health instead.

1.4.2 Proposed classification

Based on the data available, PTBBA should be classified as

N; R51/R53

Reprotoxic Cat. 2

T	Toxic
R 60	Possible risk of impaired fertility
R 22	Harmful if swallowed

R 48/23/24/25 Toxic by inhalation, in contact with skin and if swallowed

Based on the available LD50 values, 4-tert-butylbenzoic acid is to be classified "Xn, harmful" and labelled with "22, Harmful if swallowed".

The target organs for repeat dose toxicity of 4-tert-butylbenzoic acid were the central nervous system, liver, kidneys, testes, epididymides, hemopoietic system and the thymus. Similar lesions in the liver, kidney, male reproductive organs and peripheral blood were identified across all studies regardless of the route of exposure. Neurotoxicity was produced after repeated inhalation and oral administration. No clinical signs of abnormal neurobehaviour or morphological abnormalities of nervous tissues were reported from the dermal study. The fact that nervous tissue damage has not been observed in the dermal study is no proof for the absence of neurological effects since methods applied in all repeat-dose studies are routine staining procedures which may be insufficient to detect specific lesions in cellular compartments of the nervous system. Based on these data, 4-tert-butylbenzoic acid should be classified “T, R48/23/24/25, Toxic by inhalation, in contact with skin and if swallowed”. The adverse effect levels were far below the guidance values for the classification as harmful. Therefore the currently applied classification should be replaced.

The substance should be classified as a reproductive toxicant T, Repr. Cat 2 and labelled with R 60 (possible risk of impaired fertility) since a clear-cut toxic potential specifically adverse to male gonads and resulting in impaired male fertility in rats was revealed for PTBBA repeatedly in several studies and consistently across various routes of administration.

Based on the data available, PTBBA should be classified as: N; R51/R53.

PTBBA is not readily biodegradable according to the available data and therefore R53 classification is proposed. The lowest results from the available aquatic ecotoxicity studies were found by Bridie et al. (1979b) for fish (*Caracassius auratus*). The study demonstrates the pH dependency of ecotoxicity. At pH 5 an LC_{50} of 4 mg l^{-1} and at pH 7 an LC_{50} of 33 mg l^{-1} were found indicating that the substance is toxic at a pH range which is relevant for the aquatic environment and therefore the phrase R51 is proposed.

The proposal for the above mentioned classification has been submitted to the TC C&L in November 2004. At the Meeting on Environmental Effects of Existing Chemicals, Pesticides and New Chemicals, Commission Working Group on the C&L of Dangerous Substances has concluded that the substance will be classified as N, R50-53.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

Details of the production methods are confidential.

2.1.2 Production capacity

The production of PTBBA in the EU was ceased by the year 2006.

2.1.3 Tonnage

Detailed information on the current EU market volume and use of PTBBA has been disclosed to the rapporteur. Due to the relatively small market volume of PTBBA and because only few companies are involved in the production and processing of PTBBA, actual figures on production, import and export volumes are confidential (see confidential Appendix A). The approximate EU market supply of PTBBA is in the range of 2000 – 4000 t/a. Two HPV-scale importers and one LPV-scale importer operate at the moment. One company is exporting PTBBA outside the EU.

2.2 USES

2.2.1 Introduction

Industry has estimated that approximately 80 % of the EU's annual market volume is used by about 30 customers. The two main EU market suppliers have identified three uses of PTBBA and estimated their shares of the EU market. The data are included in confidential Appendix A and do not support open downstream uses.

According to industry information, PTBBA is mainly used in the EU as thermal stabiliser in PVC. For this purpose, PTBBA is first converted into PTBBA metal salts (Metal-p-tert-butylbenzoate, Me-PTBB). P-tert-butylbenzoate ion remains in the stabilising reaction unchanged. Since both PTBBA and its metal salts are present in their ionised form (as p-tert-butylbenzoate) under environmental conditions, the transformation into metal salts does not change the identity of the substance to which the environment is exposed. Consequently, the downstream use in PVC is covered by this risk assessment.

The second most important use of PTBBA in the EU is as process regulator (chain stop agent) in polymers industry for producing alkyd and polyester resins. A minor amount of PTBBA is furthermore used as intermediate in chemical industry for producing esters of PTBBA.

According to industry, PTBBA is not employed in consumer applications. The two main EU market suppliers of PTBBA state that open applications are not supported, i.e. applications where industrial users can come into contact with PTBBA, for example in cutting fluids for industrial use. However, different national registers list products which contain PTBBA:

The Nordic Product Register SPIN 1.0 lists for Denmark for the year 2000 seven products of "paints, lacquers and varnishes" using PTBBA in a quantity of 0.1 tons. Six products of these were registered under the industrial use category of "sale, maintenance and repair of motor vehicles and motorcycles".

In Norway, the most frequent use of the registered products is the use in paints and varnishes. The most frequent industrial use category in Norway is construction (SPIN further gives "manufacture of basic metals" as a frequent category). The Norwegian Product Register contained all together seven products with a PTBBA content of 0-1 % and a total volume of 2 t, and 19 products with a PTBBA content of 1-10 % and a total volume of 18 t.

The Swedish Product Register (information from the year 2001) contains altogether four PTBBA products. The specified uses were "corrosion inhibitors" and "raw material for synthesis". The industrial categories reported were "fabricated metal products" and "industry for other organic basic chemicals". SPIN gives for the quantity in Sweden 27 tons.

The Finnish Product Register did not contain any entries for PTBBA in April 2002. Of the four national Nordic Product Registers, only the Norwegian Product Register (as April 2002) contained products in consumer use (no information on the use category provided).

The Swiss Product Register (status September 2002) contains the following products for professional uses: one product as corrosion inhibitor (concentration 10-50 %), one product for use in paints, two products as process regulator and two products for photochemicals (concentration 1-10 %). Furthermore, consumer use may occur in the case of one product used as washing agent and two products used as process regulator (concentration 0.1 –1 %). According to updated information of the Swiss Product Register (December 2006) the one product which was assigned to the consumer use (previously, September 2002) is not any more available.

On the basis of the information above, consumer uses are assumed to make a negligible part of the tonnage. Consequently, they are not included in the assessment.

2.2.2 Scenarios

2.2.2.1 Production

The production in the EU was ceased by the year 2006. A local scenario for a generic production site is included for information only.

2.2.2.2 Use as intermediate

PTBBA is used at one site as intermediate. According to the site specific information, emissions from this site are negligible.

2.2.2.3 Use as stabiliser in PVC (production of PTBBA metal salts)

PTBBA is converted into its metal salts in the manufacture of liquid mixed metal stabilisers. In the first stage, a mixture of salts of different acids are produced in a one pot reaction. Organic acids, including PTBBA, are reacted with mixed metal oxides or hydroxides in a non-aqueous medium in a closed system. The small amount of process water, resulting from the salification reactions, is removed from the mixture by distillation. This process water, which contains only small amounts of PTBBA, is treated before being discharged to sewer in agreement with local authorities or collected separately for incineration. In the second phase, other additives are added to the mixture. The final liquid stabiliser preparation is transported in containers to the users in the PVC industry (ESPA, 2006). This life-cycle stage is considered to occur in chemical industry (IC 3).

2.2.2.4 Use as stabiliser in PVC (compounding and conversion)

According to ESPA (2006), the next two life-cycles stages (compounding and conversion) occur generally at one site. The mixed metal stabilisers are used entirely in the processing of plasticised PVC. ESPA (2006) indicates that liquid metal stabilisers are used in the both major compounding methods and their subsequent conversion methods. Dry blending followed by calendering is the major use of these stabilisers. Other uses are injection molding (e.g., to footwear) and extruded tubing (e.g., garden hoses) made of the dry blend. The main plastisol blend use is flooring obtained by spread coating.

The emission scenario document on plastics additives (OECD, 2004) presents highest emission factors for a plastics processing site for dry blending followed by calendering. A local scenario for this type of process is presented in the following sections as the realistic worst case scenario for the processing step of Me-PTBB in the plastics industry.

2.2.2.5 Use as stabiliser in PVC (service life)

The chemical reaction in the heat stabilising process of PVC is the binding of metal ion with chloride escaping from the polymer due to thermal deterioration. P-tert-butylbenzoate ion is expected to remain in this process unchanged in the polymer matrix. Hence, releases during service life occur and they are estimated in the following chapters.

2.2.2.6 Use as stabiliser in PVC (disposal)

The emission scenario document on plastics additives (2004) suggests that for disposal stage the emissions to air are zero both for landfilling and incineration. Releases to surface water or groundwater due to leaching are likely to occur but no quantitative information is available.

2.2.2.7 Use as modifier in resins (processing)

The use of PTBBA as a chain stop agent in resins leads to improved properties of the resin (e.g. drying behaviour, hardness, solvent resistance). PTBBA is added into the polymerisation step of resin production where it reacts covalently with the usual alkyd monomers (Jones, F., 2003). This use is hence an intermediate use. According to industry, PTBBA is added into the mixture of precursors in a share of 1-10 % w/w, but unreacted PTBBA is present only in very low concentrations (< 0.1 % w/w). It is therefore assumed that the downstream uses of resins are not relevant for the environmental risk assessment.

2.3 LEGISLATIVE CONTROLS

PTBBA is not subject to substance specific legislation in the EU.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

The release estimation and calculation of environmental concentrations was carried out with EUSES 2.0.3. PTBBA is expected to be to a large extent present in its ionic form p-tert-butylbenzoate in the environment. The release factors, however, apply to the non-dissociated form. For the sake of transparency and simplicity, the molecular weight of PTBBA is applied for calculations throughout. The incorporation of the molecular weight of the ionic form would not be of relevance for the conclusions as the difference in molecular mass between the undissociated and dissociated forms of the molecule is 1 molecular mass unit due to the loss of a proton.

3.1.2 Environmental releases

It must be noted, that the market volume does not have much influence in this assessment on the local exposure assessment due to the use of specific local information and the use of the emission scenario document on plastics additives.

According to the physical-chemical properties of PTBBA, the substance will mainly be released to water and air, whereas releases into soil via sludge application are negligible. Specific information on releases was received from intermediate processing sites and from sites manufacturing mixed metal stabilisers for the use in PVC. In addition, information on the uses of mixed metal stabilisers in PVC was provided to the rapporteur.

3.1.2.1 Release from production

PTBBA production at the only European production site ceased in 2006. A generic production site scenario is presented here for background information, only. A production of 3000 t/a and no further processing on site is assumed as the basis for calculation. According to the TGD, the generic emission factor into waste water is 0.003 (wet process) and to industrial soil 0.00001 (Table A 1.2). The emission factors into surface water (direct release) and air are zero. The resulting release to waste water is 9 t a^{-1}. It should be noted, that the overall release factor of the former production plant was < 0.00006, which is more than a factor of 50 lower than the generic estimate.

3.1.2.2 Release from industrial/professional use

Use as intermediate

According to industry, the only use of PTBBA as intermediate in chemical industry is for producing esters of PTBBA (mostly methyl and vinyl esters). The esterification process is only conducted by one company which reported negligible emission into air and surface water. Hence, for this use, no exposure estimates are derived. The confidential information

can be made available to Member States Competent Authorities, as a confidential annex, on request. In March 2007 the company stopped using PTBBA as intermediate.

Use as stabilizer in PVC – production of liquid mixed metal stabilisers

The European Stabiliser Producers Association provided information on releases (ESPA, 2006). Liquid mixed metal stabilisers are manufactured using a non-aqueous method but a small amount of water is formed during the process. This water is removed from the mixture by distillation and treated before discharge to sewer or collected for incineration.

According to ESPA (2006) six plants are using PTBBA for the production of liquid mixed metal stabilisers. For five of them information was provided. Release estimates based on measured data from waste water effluents after pretreatment but before discharge to the sewer were provided by three companies (sites 1 to 3). Other information applicable for the release estimation was provided, too. The volume of the sites 1 to 4 should cover > 90 % of the use volume of PTBBA for stabiliser manufacture. According to ESPA (2006), all sites use the same processing technology. No information on the days of operation per year was provided. For the realistic worst case estimation of annual releases, the number of emission days is assumed to be 330 d a^{-1} (the release data for sites 1 to 3 were given as kg d^{-1}). The emissions from site 6 are according to ESPA not expected to differ from the emissions of the other sites. The release to waste water for site 6 is therefore set to the same value as the relase of the site 3 (note that the TGD gives an emission factor of zero for this use (IC3, UC 33, MC Ic). From Table A3.3 of the TGD, EF_{air} of 0 is obtained. Emissions to air from other sites are also assumed to be zero in the line with the TGD and information provided by ESPA (2006).

Table 3.1 Releases of PTBBA from the stabiliser production sites.

	Release (kg a^{-1})	
	To waste water	**To air**
Stabiliser production site 1	0.4	0
Stabiliser production site 2	3.0	0
Stabiliser production site 3	9.2	0
Stabiliser production site 4	0 (waste incinerated)	0
Stabiliser production site 5	0 (No waste water releases)	0
Stabiliser production site 6	9.2	0
Total	21.8	0

The release of the site 6 is allocated to the region.

Measurements of PTBBA concentrations in effluent have been carried out by the sites 1 to 3 using the method of Clariant (2006). An acidification before analysis converts p-tert-butylbenzoate (the dissociated form of PTBBA) to PTBBA. Thus a concentration covering both species is measured.

Use as stabilizer in PVC – compounding and conversion

According to ESPA (2006), the usual processing methods in the PVC industry where liquid mixed metal stabilisers are involved are completely dry and the cleaning is carried out by vacuuming so that no releases to waste water occur. However, according to the emission scenario document (ESD) on plastics additives (OECD, 2004) releases to waste water and air can be expected from the processing methods in question (see Table 3.2).

Information on the types of compounding and conversion applicable for liquid metal stabilisers has been provided by ESPA (2006; see chapter 2.2.2.4). However, no quantitative information on the amount of PTBBA used for different types of compounding and conversion processes is available. Therefore it is assumed that the whole tonnage of PTBBA used in PVC is compounded by dry blending followed by calendering in the same plants. This processing combination results in the highest emission factors in total for PTBBA, which belongs to the high volatility group (no information is available on the volatility of Me-PTBB). According to the ESD, the releases from dry blending and calendering occur initially to air, but part of the release may end up into waste water due to condensation. Industry has not provided any further details on processes and release abatement than those presented in the ESD. Therefore, the release factors provided in the ESD are applied.

Table 3.2 The release factors for plastics industry.

	Emission factor	
	To waste water	**To air**
Handling	0.0001	0
Compounding (dry blending)	0.00025	0.00025
Calendering	0.00125	0.00125
Total	0.0016	0.0015

Due to the confidentiality of the total use volume in PVC, the resulting total releases are kept confidential (the confidential information can be made available to Member States Competent Authorities, as a confidential annex, on request.). For this use, 10 % of the volume is assumed to be processed in the region.

Use as modifier in resin production

According to industry, the polymerisation process of resins where PTBBA is used as chain stop agent is not causing environmental releases. According to a customer, any resulting waste water or waste from the process and cleaning operations is incinerated.

3.1.2.3 Release during service life and disposal

Releases from the use and disposal of PVC can be expected to occur. The emission scenario document (ESD) on plastics additives (OECD, 2004) gives release factors for “volatiles” (PTBBA belongs to the high volatility group according to the ESD) for indoor and outdoor uses. As a realistic worst case estimate, the release factors for outdoor use are applied. A

service life of ten years is assumed for the end uses of flexible PVC on the basis of the ESD, Table 4.3. The resulting emission factors are: F_{water} = 0.16 % (annual release), F_{air} = 0.005 % (annual release). According to the equation 10 of the TGD, total release is estimated as the product of the annual release fraction, annual use volume and service life. The release estimates are kept confidential. The release estimates are used for the calculation of regional and continental concentrations. Ten percent of the use is assumed to occur in the region.

According to the ESD, at least 75 % of plastics are not recycled or used in incinerators and thus can be assumed to be landfilled. Accordingly, as no specific information on end uses is available, at least 75 % p-tert-PTBB) present in PVC products are expected to be landfilled. Release from landfills can be assumed to occur to water via leaching, if any. As the annual volume of PTBB contained in PVC is reasonably low (the confidential information can be made available to Member States Competent Authorities, as a confidential annex, on request.), it can be expected that exposure at local level is negligible. For air, a release factor of zero is given in the ESD.

3.1.2.4 Other sources

PTBBA is known as a characteristic photodegradation product of the most common UVA filter Parsol 1789 (CAS 70356-09-1; 4-tert-butyl-4'-metoxydibenzoyl methane; BM-DBM), which is used in sun creams (Roscher et al., 1994; Schwack and Rudolph, 1997). Some releases to surface water and waste water can be expected to occur from this source. These releases are, however, assumed to be minor in the frame of this assessment.

MacNamara et al. (1995) found PTBBA in whiskey spent lees in an investigation looking at the flavour compounds. No quantitative information is given and neither analysis of the origin of the compounds found was presented. Releases from this source are assumed to be negligible.

3.1.2.5 Summary of releases

Table 3.3 lists the expected regional and continental releases from each life cycle step. Due to the confidentiality of the use volumes, the release estimates of some scenarios are kept confidential (the confidential information can be made available to Member States Competent Authorities, as a confidential annex, on request.).

Table 3.3 Releases of PTBBA to waste water and air allocated to the region and continent.

Scenario	Regional emission (kg a^{-1})		Continental emission (kg a^{-1})	
	To waste water	To air	To waste water	To air
Intermediate processing (IC 3 / UC 33)[5]	0	0	0	0
Use as stabiliser in PVC				
- production of PTBBA metal salts (IC 3 / UC 33)	9.2	0	12.6	0
- compounding and conversion	see Appendix A	see Appendix A	see Appendix A	see Appendix A
- service life	see Appendix A	see Appendix A	see Appendix A	see Appendix A
Use as modifier in resin production (IC 11 / UC 43); processing (polymerisation step)	0	0	0	0

3.1.3 Environmental fate

3.1.3.1 Degradation in the environment

Ready biodegradability of PTBBA was investigated in an OECD 301D closed bottle test and in an OECD 301B modified Sturm test.

The closed bottle test was carried out with a nominal concentration of 3 mg l^{-1} PTBBA. PTBBA was added to the test medium emulsified with sulphonate (Dobane PT). As inoculum sludge from a municipal STP was used. This amount of PTBBA can be assumed to have dissolved completely even without emulsifier. Sodium benzoate was used as the reference substance. No biodegradation was observed at the end of the test on day 28. However, a slight degradation (6-5 % measured as oxygen consumption of the total ThOD) was observed on day 15. PTBBA caused no inhibition of microbial activity under the test conditions. The test was performed at a temperature of 21 ± 1 ºC. No pH or other conditions were recorded in the test (Shell Research Limited 1984a).

The modified Sturm test employed a nominal concentration of 20 mg l^{-1} of PTBBA. Deviating from the standard test protocol, PTBBA was added to the test medium in a stock solution emulsified in Dobane PT sulphonate. Sludge from a municipal STP was employed. The test did neither include the provisional toxicity control nor the abiotic sterile control. As the concentration of PTBBA in the closed bottle test was one order of magnitude lower, the results cannot be used to exclude a possible inhibition of microbial activity in the modified Sturm test. Test temperature is not given. No biodegradation was seen in the first 8 days in the

[5] Intermediate processing ceased in March 2007.

modified Sturm test, but after this time span the substance was degraded approximately at a constant rate. On day 28 (iterated result), 41-46% biodegradation of ThOD was observed. No pH was recorded during the measurements (Shell Research Limited 1984a).

Based on a modified MITI I Test (ready biodegradability test according to OECD 301C), PTBBA is not readily biodegradable (MITI 1992). No information regarding to the origin of the inoculum was reported. PTBBA test concentration was 100 mg l^{-1}, temperature was 25 ± 1 ºC and duration 28 days. The degree of biodegradation was 0-12 % of ThOD at the end of the test. This result should be interpreted with precaution as the concentration of PTBBA was probably beyond its water solubility. In addition, no pH was indicated.

Biodegradation of PTBBA was also measured in a BOD-standard test of the American Public Health Association (Babeu and Vaishnav 1987). Pre-adapted mixed microbial cultures were used and biodegradation was measured in at least two concentrations between 0.4-3.2 mg l^{-1} of PTBBA. Dissolved oxygen was measured on days 0, 5, 10 or 11, 14 or 15, and 20. The test was carried out at a temperature of 21 ± 3 ºC. The estimated BOD_5 (estimation from the whole data) was 28 % of ThOD.

A BOD_5-test carried out according to standard No. 219 of the American Public Health Association also confirms that PTBBA degrades very slowly (Bridie et al. 1979a). The BOD_5 was 11 % of ThOD. The test temperature was 20 ± 1 ºC, but pH or other test conditions were not reported. A COD of 98 % of ThOD was reported, measured according to standard D 1252-67 of the American Society for Testing and Materials.

3.1.3.1.1 Atmospheric degradation

No experimental data is available for atmospheric degradation. Indirect degradation via reaction with OH-radicals was estimated with AOP version 1.91. The resulting rate constant k_{OH} of 2.61 * 10^{-12} cm^3 $molecule^{-1}$ s^{-1} is used in the assessment. Using this estimate, a pseudo first order rate constant for degradation in air is calculated using EUSES 2.0: $Kdeg_{air}$ = 0.113 d^{-1}. This rate gives a half-life of 6.3 days for PTBBA in air.

3.1.3.1.2 Aquatic degradation (incl. sediment)

PTBBA does not have any functional groups which facilitate hydrolysis of the substance. No data on photodegradation in water were available. The abiotic degradation rate in water is assumed to be zero for modelling purposes.

Vaishnav and Babeu (1987) measured the biodegradation of PTBBA in groundwater (GW), river water (RW) and harbour water (HW). They sampled groundwater 12 km north of Lake Superior, river water at the surface from the Lester River in the southern St. Louis County, and harbour water at the surface at the Lake Superior's Superior Bay near Barker's Island. The water of each sample was filtered through a 1 cm thick cotton layer and aerated for 24 h until the start of the degradation test. The standard BOD method of the American Public Health Association was applied. PTBBA was added into the filtered harbour water in the concentrations of 0.0, 0.8, 1.6 and 3.2 mg l^{-1}. All PTBBA can be assumed to have dissolved in these concentrations. Biodegradation was estimated by measuring dissolved oxygen on days 0, 5, 10, 14 or 15 and 20 and determining the results as percent of ThOD. Incubations took place at 21 ± 3 ºC. General water quality of the test water was measured at the start of the experiment. Hardness was 121, 59 and 50 mg $CaCO_3$ l^{-1} and pH was 8.2, 7.7 and 7.6 for GW,

RW and HW, respectively. According to the results (see Table 3.4), PTBBA obeyed the first order biodegradation rate kinetics.

Table 3.4 Degradation of PTBBA in natural surface waters (Vaishnav and Babeu, 1987)

	Ground water	River water	Harbour water
Biodegradation rate constant d^{-1} [a]	NC[b]	0.027	0.073[c]
Half-life (d)	-	26	9.5[c]
Initial microbe cell count of the unfiltered water (cells ml^{-1})	55	420	310

a) The mean standard error for all determinations in all waters for all substances was ± 11% (the study included 10 chemicals altogether).

b) NC = not calculated. The difference between the test and control BOD values was insufficient.

c) The rates indicated according to the more accurate source of Vaishnav and Babeu (1986).

The test was also carried out in a similar manner with harbour water filtered through a 10 µm pore size filter. Vaishnav and Babeu (1986) compared the BOD_5–values from both tests with harbour water but they observed no significant difference between the two different filtering methods. Vaishnav and Babeu (1987) also measured biodegradation in ground water applying three different treatments. In the first treatment phosphate and ammonium were added to the test water (incubation of 14 days). The second treatment was an inoculum of acclimated microbes isolated from wastewater (10^5 cells into the 300 ml BOD test bottle, incubation of 5 days). The third treatment was a combination of the nutrient and microbe addition (incubation 5 days). Biodegradation was observed in all three test conditions. The biodegradation constants of PTBBA obtained were 0.029, 0.008 and 0.062 d^{-1} for the three treatments, respectively. The half-lives were correspondingly 24, 87 and 11 d.

Vaishnav and Babeu (1986) report an additional trial with the harbour water with the three similar treatments as described above. Only the third treatment (nutrients and microbes added) showed a slightly faster biodegradation (0.088 d^{-1} rate constant and 7.9 d half-life) than without treatments. However, the estimated BOD_5 for the test without treatment was 7 % of ThOD whereas the BOD_5 was 31 % and 36 % for the test with nutrient addition and for the test with nutrient and microbe addition, respectively.

3.1.3.1.3 Degradation in soil

No information is available on the degradation in soil.

3.1.3.1.4 Summary of environmental degradation

In two standard ready biodegradability tests, PTBBA failed both the 10-day window and the pass level of 60 % biodegradation of ThOD in 28 days (Shell Research Limited, 1984a). PTBBA is therefore classified as not readily biodegradable. Inherent biodegradability test results are not available, although the degree of degradation observed in the modified Sturm test (Shell Research Limited, 1984a) and in some of the other tests indicate that PTBBA might be inherently biodegradable. For modelling purposes, the biodegradation rate constant for STPs is assumed to be zero. For estimating concentrations in surface water, it is assumed that the substance is not biodegradable ($kbio_{water} = 0\ d^{-1}$). The results of Table 3.4 are not used

in modelling as the concentrations of PTBBA employed in the study were much higher than what can be expected to be found in the environment.

For soil and sediment no studies were available and thus on the basis of the results from tests on ready biodegradability, degradation is assumed to be zero for these compartments.

3.1.3.2 Distribution

PTBBA is dissociated (ionised) in the environmentally relevant pH range. Water solubility and $\log K_{ow}$, which are given for the undissociated form in Table 1.1, are very much dependent on pH. A pH of 7 is assumed according to the TGD for STPs in this assessment. For the receiving environment, exposure at pH 5 and pH 7 are calculated. This choice is pragmatic and stipulated by the ecotoxicity results of the critical study and other ecotoxicity studies indicating that at a lower pH more effects are expected probably due to the higher bioavailability of the undissociated form.

Appendix XI of the TGD presents a method for correcting i.a. the partitioning coefficients of the undissociated form against the pH in the environment. This method is in such a way simplistic, that it assumes that only the undissociated form has influence on the partitioning (and toxicity). The equation for the correction factor

$$CORR = \frac{1}{1+10^{(pH-pKa)}}$$

calculates the part of undissociated substance at the given pH. Using the equation, it can be determined that at pH 5 19 %, at pH 6 2.2 %, at pH 7 0.2 % and at pH 8.25 0.01 % of PTBBA in aqueous solution is in undissociated form.

The correction factor was applied to the K_{ow} of 2511.9 for the undissociated form ($\log K_{ow}$ 3.4). As a result, a $\log K_{ow}$ of 0.76 was obtained for pH 7. Water solubility was consequently estimated by Wskowwin v1.41 and gave 12,600 mg l^{-1}. Thus PTBBA is at pH 7 readily soluble in water. Similarly, a $\log K_{ow}$ of 2.68 and a water solubility of 288.9 mg l^{-1} for pH 5 were obtained.

The Level I v 2.11 of Mackay model was used to demonstrate the distribution in the model environment. Of the undissociated form 4.3 % in air, 56.6 % in water, 18.0 % in soil and 21 % in sediment would be found according to this model. The distribution at pH 7 is very different: 99.8 % would be found in water, and the rest 0.2 % in sediment, soil and air. It can be concluded that the distribution in the environment is dependent on the pH but in the environmentally relevant pH range PTBBA can be found almost completely in water and only insignificant amounts in air, soil and sediment.

3.1.3.2.1 Adsorption

No experimental data on adsorption is available. The K_{oc} was calculated from the QSAR regression provided for organic acids in the TGD ($\log K_{oc} = 0.60 \log K_{ow} + 0.32$), resulting in a K_{oc} of 229 ($\log K_{oc}$ of 2.36). This value applies to the undissociated form.

The K_{oc} was normalised to pH 5 and pH 7 using the corrected $logK_{ow}$ values, respectively. For pH 7, a pH–normalised K_{oc} of 6 results. This value is used in the calculation of the solid-water partition coefficients. The solids-water partitioning coefficients for pH 7 are according to the TGD as follows: Kp_{soil} = 0.119 l kg^{-1}, Kp_{sed} = 0.299 l kg^{-1} and Kp_{susp} = 0.597 l kg^{-1}.

For pH 5, a pH–normalised K_{oc} of 85 results. This value is used in the calculation of the solid-water partition coefficients. The solids-water partitioning coefficients for pH 5 are according to the TGD as follows: Kp_{soil} = 1.7 l kg^{-1}, Kp_{sed} = 4.24 l kg^{-1} and Kp_{susp} = 8.48 l kg^{-1}.

3.1.3.2.2 Volatilisation

The Henry's law constant in Table 1.1 refers to the undissociated form of PTBBA. For pH 7, the constant can be normalised with the same equation as used for normalising the K_{oc} (see section 3.1.3.2.1). For pH 7, a Henry's law constant of 5 * 10^{-4} Pa m^{-3} mol^{-1} results indicating very low volatility. Consequently, the air-water partitioning coefficient $K_{air\text{-}water}$ is 2.11 * 10^{-7} (equation 22 of the TGD). For pH 5, a Henry's law constant of 0.011 Pa m^{-3} mol^{-1} and air-water partitioning coefficient $K_{air\text{-}water}$ of 4.6 10^{-6} were calculated. It should be noted, that if these constants would have been calculated using the water solubility estimates derived in chapter 3.1.3.2 with Wskowwin, the results would have been slightly, but insignificantly, different.

3.1.3.2.3 Distribution in wastewater treatment plants

Due to the low volatility and low adsorption potential of PTBBA to organic matter, the substance is expected to remain completely in the water phase in waste water treatment plants. According to the SimpleTreat model used in EUSES 2.0.3, 100 % of the PTBBA is released to the surface water when using the PTBBA properties at pH 7. The calculated fractions going into air and sludge are < 1 %. Waste water treatment plants are well buffered, and therefore there is no need to separately calculate the distribution for pH 5.

3.1.3.3 Accumulation and metabolism

According to the very low K_{oc} in the environmentally relevant pH-range, no significant geoaccumulation is to be expected.

MITI (1992) measured bioconcentration in *Cyprinus carpio* using a method corresponding to the OECD 305 standard with test concentrations of 0.5 mg l^{-1} and 0.05 mg l^{-1}. Duration of exposure was 6 weeks, flow rate in the test 200-800 ml min^{-1} (no specific flow rate for this particular test was given in the data sheet) and temperature approximately 25 °C. The measured BCFs varied between 1.1 and < 4.6.

A BCF of 3.162 was calculated for ionic substances with a $logK_{ow}$ < 5 using BCFWIN version 2.15. The method used by BCFWIN (Meylan et al., 1998) indicates that logBCF of such compounds varied in the training set between 0 and 1. The pH corrected experimental $logK_{ow}$ is 0.76 at pH 7. At pH of 6, $logK_{ow}$ is 1.75, and at pH of 5, the $logK_{ow}$ is 2.68. On this basis, it can be expected that in the environmentally relevant pH range PTBBA has a low potential to bioaccumulate and the assessment of secondary poisoning is therefore not conducted.

3.1.4 Aquatic compartment (incl. sediment)

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

In the following chapters, PECs have been calculated for a generic scenario for production (for information only), for the specific sites manufacturing mixed metal stabilisers and for a generic plastics industry site. The $PEC_{sediment}$ has been calculated with the equilibrium partitioning method according to equation 50 of the TGD using $K_{susp\text{-}water}$ of 1.05 (pH 7) and 3.02 (pH 5) and RHO_{susp} of 1150 kg m^{-3}.

3.1.4.1.1 Calculation of PEC_{local} for production

For the local generic production scenario the default values of the TGD for the number of emission days (300 d a^{-1}) and dilution factor (40) are used. The resulting daily release is 30 kg d^{-1}, the $Clocal_{water}$ 0.075 mg l^{-1} and $PEClocal_{stp}$ 3 mg l^{-1}. These results are for backgorund information, only as production in the EU ceased in 2006. $Clocal_{water}$ is same for pH5 and pH 7.

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

Use as stabiliser in PVC – production of PTBBA metal salts

For sites 1 and 2 specific dilution factors were calculated based on the information provided. For sites 3 and 6 generic values of the TGD were applied. Although the use is considered to be intermediate processing, the dilution factor of 10 instead of 40 was applied as proposed by ESPA (2006). The resulting concentrations are presented in Table 3.5.

Table 3.5 Local concentrations in aquatic environment for the production of PTBBA metal salts.

	Sewage Treatment Plant Flow (m^3 d^{-1})	River Flow (m^3 d^{-1})	Dilution factor	$PEC_{local\ stp}$ (µg l^{-1})	$C_{local\ water}$ (µg l^{-1})		$PEC_{local\ water}$ (µg l^{-1})		$PEC_{local\ sediment}$ (µg kg^{-1} wwt)	
					pH 7	pH 5	pH 7	pH 5	pH 7	pH 5
Site 1	350 (own treatment plant)	72,000 (mean low flow)*	207	3	0.015	0.015	0.14	0.13	0.13	0.33
Site 2	2,000	2,500,000 (mean flow; one third of this is applied as mean low flow value)	418*	4.6	0.011	0.011	0.14	0.12	0.13	0.32
Site 3	2,000	Not available	10 (generic)	14	1.40	1.40	1.52	1.51	1.39	3.96
Site 4	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable		Not applicable		Not applicable	
Site 5	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable		Not applicable		Not applicable	
Site 6	2,000 (generic)	Not available	10 (generic)	14	1.40	1.40	1.52	1.51	1.39	3.96

*The flow rate of 72,000 m^3 d^{-1} has been provided by the site as "the minium river flow". This is interpreted by the rapporteur as the mean low flow, and directly used for the calculation of the dilution factor.

** The dilution of 1250 was provided by site 2 using the mean flow. The dilution factor of 418 has been calculated by the rapporteur.

Use as stabiliser in PVC – compounding and conversion

According to the emission scenario document (ESD) on plastics additives (OECD, 2004), the volume of plastics produced at one site is for open processes (such as calendering) 7350 t a^{-1}. According to industry, the fraction of PTBBA metal salt (Me-PTBB) added in PVC can be up to 1.5 % w/w. This is in line with the ESD's Appendix III, which gives a thermal stabiliser fraction of 2 % to flexible PVC (for the whole stabiliser preparation). The first two values result in a usage of 110.23 t a^{-1} of Me-PTBB at a generic site. The number of emission days for the site is assumed to be 300 d a^{-1} resulting in a release of 0.0594 kg d^{-1}. The flow of the STP to which the site is connected is 2000 m^3 d^{-1} and the dilution factor is 10 as given by the TGD.

$Clocal_{water}$ (µg l^{-1})		$PEClocal_{water}$ (µg l^{-1})		$PEClocal_{sediment}$ (µg kg^{-1} wwt)		$PEClocal_{stp}$ (mg l^{-1})
pH 7	pH5	pH 7	pH5	pH 7	pH5	0.0297
2.97	2.96	3.09	3.08	2.82	8.08	

3.1.4.2 Measured levels

Deroux et al (1996) detected PTBBA in water sampled in 1994 from canal fed by the Rhône river, France. The study included an analysis of a broad spectrum of pollutants and the authors concluded that 110 compounds were detected at the nanogram per litre level.

PTBBA was identified in the effluents from a biological treatment plant (Gulyas et al., 1993), but chemical concentrations were not specified. The pilot plant, which is located at the Technical University of Hamburg in Germany, receives domestic waste water discharges from a nearby residential area including small business enterprises like shops and restaurants.

PTBBA was found in the leachate of a Swedish landfill (Atleverket, Örebro) in concentration of 27.1 µg l^{-1} under several other pollutants (Welander, 1997). The sample was a single sample taken in July 1994. The landfill receives mainly household waste and the leachate amount was estimated at 75 000 m^3 a^{-1}. pH of the leachate was at the time of sampling 7.9 indicating that the landfill was in the anaerobic phase. PTBBA was not found at two other landfills included in the study (Filborna, Helsinborg: mixed industrial and municipal waste and Gärstad, Linköping: industrial waste and incinerator ashes).

Clark et al. (1991) analysed the effluents from three publicly owned treatment plants in New Jersey, USA. Sampling was conducted three times for each facility during a 1-year period. Two of the treatment plants are located in industrial areas and have industrial waste water contributions of 27 % and 18 %, respectively, and contained PTBBA in their effluent discharges.

Table 3.6 PTBBA concentrations in effluents from three waste water treatment plants (Clark et al. 1991).

	Facility A (rural area)			Facility B (industrial area)			Facility C (industrial area)		
Waste water characteristics	No known industrial contributor			STP volume of 316,050 $m^3 d^{-1}$, 27 % of industrial origin (pharmaceutical, yeast, paper, and chemical manufacturing)			STP volume of 874,335 $m^3 d^{-1}$, 18 % of industrial origin (mostly textile and dye manufacturing)		
PTBBA concentration ($\mu g\ l^{-1}$)	–	–	–	–	0.6	–	1.4	32	11

The Japan Environmental Agency began investigating chemical pollution in Japan in 1974. Based on the 1976-1990 annual reports entitled "Chemicals in the environment" that were produced by the Japan Environmental Agency (Office of Health Studies), Yoshioka and Youki (1993) specify a value of 0.3 $\mu g\ l^{-1}$ as the highest environmental concentration of PTBBA in Japanese waters.

3.1.4.3 Comparison between predicted and measured levels

A comparison between predicted and measured concentrations of PTBBA in the aquatic environment cannot be conducted due to the very limited availability of measured data.

3.1.5 Terrestrial compartment

3.1.5.1 Calculation of PEC_{local}

PEC_{local} for soil was calculated according to the provisions of the TGD. Emissions into soil are assumed to occur only via aerial deposition, as the amount of PTBBA ending up in STP sludge is negligible. The PECs for soil are obtained by using soil concentration averaged over 30 days. It can be assumed that direct releases to industrial/urban soil do not occur, but PECs for urban soil based on default emission factors are nevertheless included in the EUSES-documents (the confidential information can be made available to Member States Competent Authorities, as a confidential annex, on request). For details on emission factors, fractions of main source and number of emission days see section 3.1.2 and 3.1.4.

Only for the local generic scenario for the use as stabiliser at PVC compounding and conversion sites emissions to air are expected and local PECs are thus presented for this scenario, only.

$PEClocal_{soil}$ ($\mu g\ kg^{-1}$ wwt)		$PEClocal_{groundwater}$ ($\mu g\ l^{-1}$)	
pH 7	pH 5	pH 7	pH 5
0.015	0.065	0.067	0.041

3.1.5.2 Measured levels

Williams et al. (1991) investigated the migration and degradation of waste compounds in a shallow groundwater aquifer at Villa Farm, 15 km north of Coventry, England. The site

consists of a series of disposal lagoons which received a wide variety of industrial wastes for over 30 years until 1981, including oil-water mixtures, effluent treatment sludges containing heavy metals, acids and alkalis, organic solvents and paint wastes.

Aqueous samples were collected at four locations, which represented the deepest and most reducing part of the aquifer. The pH of the samples was adjusted to pH 3 and 9.5, acidic and basic componds extracted into diethyl ether and analysed by gas chromatography – mass spectrometry (GC-MS).

Phenolic compounds formed the dominant class near the lagoon, but decreased in number along the groundwater flow path while the number of aromatic carboxylic acids increased. Among these, PTBBA was detected at all four sampling stations. As carboxylic acids are not reported to have been deposited at the site, their appearance in the polluted groundwater plume may result from phenol degradation. This seems likely as the conversion of phenol into benzoic acid in the presence of CO_2 and H_2 (i.e. under anaerobic conditions) is thermodynamically favourable (ΔG^o = -40.7 kJ mol^{-1}) and has been reported for anaerobic sewage digesters. Furthermore, a study of phenol degradation in sediment cores taken from the site (Williams and Higgo, 1994) showed that benzoic acid can also be formed in anaerobic groundwater, too. As the appearance of certain carboxylated aromatic compounds was inversely related to the relative abundance of structurally similar phenols, the degradation of phenolic compounds in groundwater may have occurred via an initial stage of carboxylation under strongly reducing (methanogetic) conditions.

3.1.5.3 Comparison between predicted and measured levels

A comparison between predicted and measured concentrations of PTBBA in the terrestrial compartment cannot be conducted due to the very limited availability of measured data.

3.1.6 Atmosphere

3.1.6.1 Calculation of PEC_{local}

Only for the use as stabiliser at PVC compounding and conversion sites emissions to air have been identified in Chapter 3.1.2. The local concentrations for the generic PVC processing site are as follows.

$Clocal_{air}$ (mg m^{-3})	$PEClocal_{air}$ (mg m^{-3})
$1.65 \cdot 10^{-5}$	$1.36 \cdot 10^{-5}$

Due to the low volatility of PTBBA, the atmosphere is not considered as a target compartment in this assessment. Same concentrations have been estimated for pH 7 and pH 5.

3.1.6.2 Measured levels

Measured data are not available for the compartment air.

3.1.7 Secondary poisoning

Due to the very low bioaccumulation potential, no assessment of secondary poisoning is considered necessary.

3.1.8 Calculation of $PEC_{regional}$ and $PEC_{continental}$

For the calculation of background concentrations, a market volume of 3,000 tpa has been used. Due to the confidentiality of the market shares of the uses, regional and continental releases are presented in the confidential Appendix only. The calculation uses the default characteristics of the TGD for the standard regional and continental environments. Table 3.7 presents the resulting regional and continental concentrations.

Table 3.7 $PEC_{regional}$ and $PEC_{continental}$.

	$PEC_{regional}$ (pH 7)	$PEC_{regional}$ (pH 5)	$PEC_{continental}$ (pH 7)	$PEC_{continental}$ (pH 5)
Surface water, dissolved (mg l^{-1})	$1.26 \cdot 10^{-4}$	$1.12 \cdot 10^{-4}$	$3.9 \cdot 10^{-5}$	$3.2 \cdot 10^{-5}$
Sediment, total (mg kg^{-1} wwt)	$1.02 \cdot 10^{-4}$	$0.3 \cdot 10^{-3}$	$3.1 \cdot 10^{5}$	$8.5 \cdot 10^{-5}$
Air, total (mg m^{-3})	$2.4 \cdot 10^{-9}$	$2.53 \cdot 10^{-8}$	$1.5 \cdot 10^{-10}$	$6.4 \cdot 10^{-9}$
Agricultural soil, total (mg kg^{-1} wwt)	$4.6 \cdot 10^{-6}$	$7.39 \cdot 10^{-6}$	$2.8 \cdot 10^{-7}$	$1.8 \cdot 10^{-6}$
Porewater of agricultural soil (mg l^{-1})	$2.1 \cdot 10^{-5}$	$4.58 \cdot 10^{-6}$	$1.3 \cdot 10^{-6}$	$1.1 \cdot 10^{-6}$
Natural soil, total (mg kg^{-1} wwt)	$9.5 \cdot 10^{-6}$	$7.14 \cdot 10^{-6}$	$2.8 \cdot 10^{-7}$	$1.8 \cdot 10^{-6}$

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

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity test results

3.2.1.1.1 Validity of the available data

For pH of 7, water solubility of 12, 600 mg/l has been estimated. Water solubility decreases with decreasing pH. In all available tests on aquatic toxicity of PTBBA except one algae test, only the nominal concentration of the substance is reported. In addition, some test reports do not provide information on pH-range and hardness of water. However, the solubility and also the ecotoxicity of PTBBA (as an organic weak acid) are strongly dependent on pH and the buffering capacity of the solution. Most of the studies were at least partly carried out in concentrations around water solubility of PTBBA as observed in the tests and without using any dissolving agents. These tests are considered not assignable with regard to their validity, but their results can be considered as upper limit for the actual acute toxicity. All tests are reported to use pure PTBBA as test substance.

3.2.1.1.2 Fish

Acute toxicity

The acute toxicity of PTBBA to rainbow trout (*Salmo gairdneri*) was examined in a semi-static water test according to EPA standards for acute toxicity testing with fish, macro-invertebrates and amphibians (EPA-660/3-75-009). Fish were exposed for 96 h with daily renewal of the test water (temperature: 13-17 °C; pH: 7.7-8.4; water hardness 230-260 mg/l as $CaCO_3$; concentration of dissolved oxygen: 10-10.5 mg/l). Six test concentrations ranging nominally from 20 to 1000 mg/l were used. The test substance was not wholly dissolved at all test concentrations and figures are expressed in terms of the amount initially added to the test vessels. The 96 h-LC_{50} was estimated by graphical interpolation using log/probit graph paper (APHA, 1980) to be 320 mg/l (Shell Research Limited, 1984b). Due to the fact that test substance was not completely dissolved in the vessels, the effective concentrations of the test are lower than the nominal concentrations and the result should be considered as an upper boundary only.

Yoshioka and Youki (1993) summarised data of several chemicals in the environment of Japan derived from the annual reports of the Japanese Office of Health Studies 1976-1990. Fish acute toxicity tests were carried out according to OECD test guideline 203 with Red killifish (*Oryzias latipes*) under semi-static conditions at 20 ± 1 °C. The concentration of dissolved oxygen was kept at more than 60 % of the saturation value. The hardness was approximately 40 mg/l and pH was 7.2. Five concentrations spaced by a constant factor of 1.8 were tested. If necessary, dimethylsulfoxide (DMSO; vehicle) and/or dispersant (HCO-40; Nikkou Chemicals Co., Japan) were added. The LC_{50}-values were determined after 48 h and 96 h of exposure. A 96 h-LC_{50} of 70 mg/l (based on nominal concentrations) was found.

Bridie et al. (1979b) examined the acute toxicity of several petrochemicals to goldfish (*Carassius auratus*). The toxicity test with PTBBA was conducted in accordance with the guidelines laid down by the American Public Health Association (APHA 1971) for static-tank toxicity tests. Fish were exposed at 20 ± 1 °C. The duration of the tests were 24 or 96 h and the solutions were aerated throughout the test period. According to the authors, the concentrations of the chemical in test solutions were determined before and after each test. However, the measured concentrations are not reported and thus the test concentrations should be regarded as nominal. Solutions were made in local tap water. The test solution was not buffered and therefore pH was measured at the toxic concentration levels. Results of the study are denoted in Table 3.8. The study demonstrates well the likely dependency of toxicity on pH. This study is not well documented and thus valid with restrictions.

Table 3.8 Acute toxicity in fish (*Carassius auratus*) by Bridie et al. (1979b).

Exposure period [h]	pH	Effect cocentration [mg/l]	Endpoint
24	5	24 h-LC_{50} = 4	mortality
24	7	24 h-LC_{50} = 33	mortality
96	5	96 h-LC_{50} = 4	mortality
96	7	96 h-LC_{50} = 33	mortality

Long-term toxicity

No long-term experimental data is available for fish.

Jobling et al. (1995) investigated several pollutants on their estrogenicity. As a screening method, direct binding of i.a. PTBBA to rainbow trout estrogen receptor was measured using liver cytosolic extract as the receptor medium. PTBBA was not found to compete with 17ß-estradiol. From the method and results only a summary has been provided and therefore its validity cannot be judged.

3.2.1.1.3 Aquatic invertebrates

Acute toxicity

The effects of short-term exposure of *Daphnia magna* to PTBBA were examined in a static test according to EPA standards for acute toxicity testing with fish, macro-invertebrates and amphibians (EPA-660/3-75-009). Daphnids were exposed for 48 h without renewal of the test water (temperature: 17.7-22°C; pH: 5.4-8.2; water hardness 160 mg/l as $CaCO_3$; concentration of dissolved oxygen: 8.2-9.1 mg/l). Two logarithmic series of concentrations of PTBBA ranging from 50 to 1000 mg/l and 1 to 50 mg/l were tested. Concentrations below 50 mg/l were completely dissolved by employing ultrasound. Effect values were calculated using probit analysis and are expressed in terms of the amount initially added to the test vessels (Shell Research Limited, 1984b). Due to the variation of test conditions, this test is regarded as valid with restrictions. Values of pH were not reported in detail and thus it is not possible to analyse whether pH varies only in the dishes with added PTBBA or in controls as well. The variability of pH is probably caused by the dissociation behaviour of PTBBA.

Table 3.9 Acute toxicity in invertebrates (*Daphnia magna*)

Exposure period [h]	Effect concentration [mg/l]	95%-CI [mg/l]	Endpoint
24	24 h-EC_{50} = 47	39 - 56	immobilization
48	48 h-EC_{50} = 24	20 - 27	immobilization

The results of another short-term toxicity test with *Daphnia magna* were published by Yoshioka and Youki (1993). The study was conducted according to OECD guideline 202 (Daphnia sp., acute immobilisation test). A 24 h-EC_{50} of 24 mg/l was reported. More detailed information on the test procedure is not available. Due to the poor documentation of the results, this test is considered regarding to its validity as not assignable.

Long-term toxicity

Yoshioka and Youki (1993) published the result of a long-term study with *Daphnia magna* carried out according to OECD guideline 202 (Daphnia sp., reproduction test). The duration of the test was 14 d, more detailed information is not available. A 14 d-NOEC of 0.75 mg/l was derived from this study. Due to the poor documentation of the results, this test is considered regarding to its validity as not assignable.

3.2.1.1.4 Algae

Acute toxicity

The acute toxicity of PTBBA to the planktonic algae S*elenastrum capricornutum* was determined in a 4 day growth inhibition test (*Selenastrum capricornutum* (Prinz) algal bottle test, EPA-600/9-78-018). Five test concentrations in the range from 1.0 to 20 mg/l were used. Cell density of the algae was measured after 2 and 4 days of incubation using a Coulter counter. The temperature during the test was 22-26 °C and pH was 7.6-4.7. The test substance was not wholly dissolved in some of the test vessels, but all concentrations below 9.5 mg/l were completely dissolved. The 96 h-EC_{50} of 2 mg l^{-1} was calculated by probit analysis and is expressed in terms of the amount of PTBBA initially added to the test vessels (Shell Research Limited, 1984b). Due to the large variation of pH, this test should be regarded as not valid. Values of pH were not reported in detail and thus it is not possible to analyse whether pH varied only in flasks with added PTBBA or in controls as well. As far as possible to judge, the algae growth in the six control flasks did not show significant variation between the controls. The variability of pH is probably caused by the dissociation behaviour of PTBBA. PTBBA's toxicity is expected to increase when pH decreases and thus the results can be assumed to reflect the actual ecotoxicity.

RCC (2006) conducted a 72-hour toxicity test using the green algae *Pseudokirchneriella subcapitata*. The test was carried out according to the OECD 201 test guideline (1984) and the Directive (EEC) 92/69, C 3, and applying GLP.

Additions to prepare synthetic test medium were made according to the OECD 201 standard. The medium had a calculated hardness of 24 mg l^{-1} as $CaCO_3$. The test water was buffered with 6 mmol l^{-1} 4-(2-hydroxymethyl)-1-piperazineethansulphonic acid. A dispersion of PTBBA was prepared using 15 minutes ultrasonic treatment after which the dispersion was stirred at room temperature in the dark over 24 hours. After stirring, the dispersion was filtered through a 0.45 µm pore size filter to remove non-dissolved particles. The nominal test concentrations prepared by dilution of the filtrate were 4.3, 9.5, 21, 43 and 94 mg l^{-1}. Three replicates were run for each test concentration and six replicates for the control. Concentration of PTBBA was measured from the test medium at the start and the end of the test by Clariant (2006) and it was between 95 % and 100 % of the nominal concentrations. The measured test concentrations (mean of the concentrations at the start and the end) were 4.2, 9.5, 21, 43 and 94 mg l^{-1}. These values were used for the estimation of the effect levels. PTBBA was also analysed from the control vessels (0 mg l^{-1}). The analysis method measured the total concentration of dissolved PTBBA (including thus both species) and the samples were taken for analysis from the test medium without algae. The cells were growing during the test exponentially, temperature was 22 °C, pH was at the start 7.7-7.9 and at the end 8.6-8.8. Appearance of the test media was monitored four times during the test and no anomalies were observed. The test laboratory conducts positive control tests at least once a year with potassium dichromate for which the last result for 72-h EC_r50 was 1.7 mg l^{-1} (between the years 2000 and 2005 72-h EC_r50 has been 0.71-1.74 mg l^{-1}).

For PTBBA, an EC_r50 > 94 mg l^{-1} was estimated. EC_r10 was estimated but not plausible, while the 95 % confidence limit could not be determined. No effects were observed up to and including 21 mg l^{-1}. The lowest concentration where effects were observed was both for growth rate and biomass 43 mg l^{-1}. The test is well documented and valid. It should be noted that in the pH range of the test PTBBA has been completely (> 99.9 %) in its dissociated form and lower effect values could be expected at lower pH.

Table 3.10 Acute toxicity in algae

Test species	Exposure period [h]	Effect concentration [mg/l]	95%-CI [mg/l]	Endpoint	Reference	Validity
Selenastrum capricornutum	96	96 h-E_rC_{50} = 2	1.8 – 2.1	growth rate	Shell Research Limited, 1984b	Not valid
	96	96 h-NOEC = 1	-	growth rate		
Pseudokirchneriella subcapitata (=S.capricornutum)	96	96 h-E_rC_{50} > 94	-	growth rate	RCC Ltd., 2006	Valid
	96	96 h-NOEC = 21	-	growth rate		

Meene et al. (2002) analysed pH-dependence of toxicity of two phenol derivatives (3,4-dinitrophenol and bromoxynil) in tests with green algae *Scenedesmus vacuolatus*. Toxicity of both substances increased with decreasing pH. The change in the toxicity along the test range of pH (ca 5.7- 7.5) was different for each substance and the authors concluded that this was probably due to different dissociation constants and very different toxicities of each species.

3.2.1.1.5 Predicted ecotoxicity (QSARs)

The QSAR-program of the Danish EPA (2006) allocates PTBBA into a class of "neutral organics –acid". The program predicts a 96h LC_{50} of 7.9 mg l^{-1} for fathead minnow, a 48h EC_{50} of 2.2 mg l^{-1} for Daphnia magna and EC_{50} of 9.9 mg l^{-1} for green algae.

In addition, ecotoxicity was estimated using ECOSAR v0.99h. The program allocates PTBBA to the same class as above and predicts a 96h LC_{50} of 28.0 mg l^{-1} for fathead minnow, a 48h EC_{50} of 34.0 mg l^{-1} for Daphnia magna and 96h EC_{50} of 23.5 mg l^{-1} for green algae.

As both QSAR-programs estimate the ecotoxicity using the "neutral organics"–models which do not differentiate between the species, these results should be considered as background information, only.

3.2.1.1.6 Microorganisms

PBBTA was tested by RCC Ltd. (2003) according to test guideline OECD 209 with a contact time of 3 hours. The source of the inoculum was a waste water treatment plant which treats predominantly domestic wastewater. The inoculum concentration was 0.92 g dry material per litre. 5 concentrations of PBBT were tested ranging from 10 to 1000 mg/l. The test substance was directly weighed in followed by ultrasonic treatment for 15 minutes and stirring over 24 hours to ensure maximum dissolution. The reference substance was 3,5-dichlorphenol. All validity criteria were met. Under the conditions of this test no significant inhibition was determined at the second highest test concentration of 320 mg/l. Only the highest test concentration of 1000 mg/l resulted in a significant inhibition of 43.5 %. A NOEC of 320 mg/l and an EC_{50} > 1000 mg/l were deduced. The calculated EC_{20} of 491 mg/l could not be validated as it was not possible to calculate the 95 % confidence limits.

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

In a respiration inhibition test with activated sludge, a NOEC of 320 mg/l and an EC_{50} > 1000 mg/l were determined. An assessment factor of 10 is applied to obtain the $PNEC_{microorganisms}$.

Therefore: **$PNEC_{microorganisms}$ = 320 mg l^{-1} : 10 = 32 mg l^{-1}**

Approximately 20 % of PTBBA is expected to be in non-dissociated form at pH 5, whereas at pH 7 > 99 % is dissociated. The non-dissociated form is the significantly more toxic form. The difference of the toxicity of the two molecular species (dissociated and undissociated) is not known but on the basis of the algae test of RCC Ltd (2006) the dissociated form also causes some of the toxicity. In order to reflect the toxicity dependence of pH, the results of the test with goldfish *Caracassius auratus* (LC_{50} of 4 mg l^{-1} for pH 5 and LC_{50} of 33 mg l^{-1} for pH 7) are used for the derivation of the PNEC. The test is not documented according to the present standard requirements, but on the basis of the other data presented in chapter 3.2.1, the results can be considered plausible. An assessment factor of 1000 is applied to these values.

Therefore:

$PNEC_{water}$ (pH 5) = 4 mg l^{-1} : 1000 = 4 µg l^{-1}

$PNEC_{water}$ (pH 7) = 33 mg l^{-1} : 1000 = 33 µg l^{-1}

3.2.1.3 Toxicity test results for sediment organisms

No experimental results with benthic organisms are available.

3.2.1.4 Calculation of Predicted No Effect Concentration (PNEC) for sediment organisms

As no experimental results with benthic organisms are available, the $PNEC_{sed}$ is calculated from the $PNEC_{water}$ according to the equilibrium partitioning method (eq. 70) in the TGD using the sediment-water partitioning coefficients and $PNEC_{water}$ at each pH, respectively.

Therefore:

$PNEC_{sediment,\ calculated}$ (pH 5) = 10.5 µg kg^{-1} wwt

$PNEC_{sediment,\ calculated}$ (pH 7) = 30.1 µg kg^{-1} wwt

3.2.2 Terrestrial compartment

3.2.2.1 Toxicity test results

No data on adverse effects of PTBBA on terrestrial organisms are available.

3.2.2.2 Calculation of Predicted No Effect Concentration (PNEC)

The $PNEC_{soil}$ is derived according to the equilibrium method of the TGD (eq. 72) using the soil-water partitioning coefficients and $PNEC_{water}$ at each pH, respectively.

Therefore:

$PNEC_{soil, calculated}$ (pH 5) = 6.45 µg kg^{-1} wwt

$PNEC_{soil, calculated}$ (pH 7) = 7.36 µg kg^{-1} wwt

3.2.3 Atmosphere

No data on adverse effects via atmosphere are available.

3.3 RISK CHARACTERISATION [6]

3.3.1 Aquatic compartment (incl. sediment)

A $PNEC_{water}$ of 4 µg l^{-1} for pH 5 and 33 µg l^{-1} for pH 7 have been derived from acute ecotoxicity data. As the pH of the receiving water bodies of the sites included are not known, the risk ratios are calculated using PECs and PNECs for both pH-values. For the distribution in waste water treatment plants, pH of 7 was assumed for all cases.

A $PNEC_{microorganisms}$ of 32 mg l^{-1} was obtained from a respiration inhibition test.

The resulting risk characterisation ratios (RCR) are presented in Table 3.11.

Both $PEC_{sediment}$ and $PNEC_{sediment}$ have been derived with the equilibrium partitioning method. Consequently, the risk ratios for sediment are equal to the risk ratios for water.

Table 3.11 Risk characterisation ratios for the aquatic compartment.

Scenario	Water and sediment		Waste water treatment plant	
	RCR at pH 5 RCR at pH 7	Conclusion	RCR	Conclusion
Generic production site	18.8 2.3	For information only	0.1	For information only
Intermediate processing[7]	-	(ii)	-	(ii)
Stabiliser production site 1	0.03 0.004	(ii)	0.0001	(ii)
Stabiliser production site 2	0.03 0.004	(ii)	0.0001	(ii)
Stabiliser production site 3	0.4 0.046	(ii)	0.0004	(ii)
Stabiliser production site 4	-	(ii)	-	(ii)
Stabiliser production site 5	-	(ii)	-	(ii)
Stabiliser production site 6	0.4 0.046	(ii)	0.0004	(ii)
Use as stabiliser in PVC - generic compounding and conversion site	0.77 0.09	(ii)	0.0009	(ii)
Use as modifier in resin production (no emission)	-	(ii)	-	(ii)

[6] 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.

[7] Intermediate processing ceased in March 2007.

Region	0.03 0.004	(ii)		

- = negligible emissions to aquatic environment

Conclusions to the risk assessment for the aquatic compartment:

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.

The six sites where PTBBA is used for the production of liquid mixed metal stabilisers cause either very low or no emissions to the aquatic environment. They thus do not cause risks.

The generic scenario for PVC compounding and conversion is also covered by this conclusion.

Releases from the use as resin modifier (an intermediate use) are expected to be zero (cf. section 3.1.2.3). Therefore, no risk characterisation ratios were calculated and conclusion (ii) applies.

Conclusion (ii) also applies to the regional scenario.

3.3.2 Terrestrial compartment

$PNEC_{soil}$ of 6.45 µg kg^{-1} wwt (pH 5) and 7.36 µg kg^{-1} wwt (pH 7) have been obtained using the equilibrium partitioning method. The following table presents an overview on the risk ratios and conclusions.

Table 3.12 Risk characterisation ratios for the terrestrial compartment.

Scenario	**Soil**	
	RCR (pH 5) **RCR (pH 7)**	**Conclusion**
Intermediate processing[8]	See $RCR_{regional}$ (Table 3.11)	(ii)
Use as stabilizer in PVC - production of PTBBA metal salts, all sites	See $RCR_{regional}$ (Table 3.11)	(ii)
Use as stabilizer in PVC generic compounding and conversion site	0.01 $2 * 10^{-3}$	(ii)
Use as modifier in resin production (no emission)	-	(ii)
Region	$1 * 10^{-3}$ $6 * 10^{-4}$	(ii)

[8] Intermediate processing ceased in March 2007.

Conclusions to the risk assessment for the terrestrial compartment:

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 intermediate use of PTBBA for production of PTBBA esters at the only site carrying out this activity due to a negligible release. No risk ratio was calculated for this site.

The six sites where PTBBA is used for the production of liquid mixed metal stabilisers cause either very low or no emissions to waste water and air. As partitioning into sludge is negligible, this route does not need to be considered. Consequently, no local risks are expected for soil.

The generic scenario for PVC compounding and conversion is also covered by this conclusion.

Releases from the use as resin modifier are expected to be zero (cf. section 3.1.2.3). Therefore, no risk characterisation ratios were calculated and conclusion (ii) applies.

Conclusion (ii) also applies to the regional scenario.

3.3.3 Atmosphere

Due to the low volatility of PTBBA, emissions into the atmosphere are not considered a relevant exposure route. No ecotoxicity data are available on effects in this compartment.

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.

This conclusion applies to the all scenarios.

3.3.4 Marine environment

Risk characterisation

Marine and brackish waters have generally a pH > 7. In seawater PTBBA will be mainly in its dissociated form. As no tests are available on marine organisms, assessment factor of 10,000 is applied to the LC_{50}(ph 7) of 33 mg l^{-1} resulting a $PNEC_{seawater}$ of 3.3 µg l^{-1}.

For the marine exposure assessment, the stabiliser production sites 3 and 6 are relevant as no information on their location is given. In addition, the generic scenario for compounding and conversion of PVC needs to be assessed regarding to the risks to the marine environment.

For the three scenarios above a dilution factor of 100 is applied to the releases of waste water treatment plant effluent to the sea (instead of the dilution factor of 10 in chapter 3.1.4). No STP is assumed to be used when released to the sea. As the release to the sea is the same as to

the surface water environment (ca. 100 % was estimated to be released from the STP to surface water), and regional concentration is negligible, risk characterisation ratios are the same as for surface water.

Table 3.13 Risk characterisation ratios for the marine water

Scenario	Marine water and sediment	
	RCR	Conclusion
Stabiliser production site 3	0.046	(ii)
Stabiliser production site 6	0.046	(ii)
Use as stabiliser in PVC - generic compounding and conversion site	0.09	(ii)

PBT-assessment

PTBBA is according to standard ready biodegradability tests not readily degradable (Shell Research Limited, 1984a). Other data available indicate that PTBBA might be inherently biodegradable (see chapter 3.1.3). As the present data cannot be used to judge whether the substance is inherently biodegradable or not, the screening P-criterion can be considered to be fulfilled.

For PTBBA, no experimental results on bioaccumulation are available. The octanol-water partitioning coefficient for the undissociated substance (logKow = 3.4) is below the screening criterion logKow of 4.5. As PTBBA is present in the environmentally relevant pH-range mainly in ionized form, bioaccumulation potential can be expected to be low. It can thus be concluded that PTBBA does not fulfil the screening B-criterion.

Only acute data on the aquatic ecotoxicity of PTBBA are available (see chapter 3.2.1). Information on the toxicity of organisms in other compartments has not been presented. The lowest acute effect value (for goldfish; 96h-LC50 = 4 mg l^{-1}) is higher than the T-screening criterion of 0.1 mg l^{-1}.

PTBBA fulfils the screening P-criterion, but not the screening criteria for bioaccumulation and ecotoxicity. Therefore, PTBBA can be considered as no PBT.

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.

3.3.5 This conclusion applies for the quantitative risk characterisation for the sites possibly located at the sea and it also covers the PBT-assessment of PTBBA.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

53 % of the imported PTBBA is converted to PTBBA-metal salts. These salts are used as stabilisers in PVC or polyolefins. The main application of pure PTBBA is the production of alkyd resins (approx. 43 %) and the last 4 % are used as a chemical intermediate (production of pigments, anaesthetics etc.).

Detailed information see chapter 2.

For workers the inhalation and dermal routes of exposure are likely to occur.

Exposure of humans may occur by contact with sex toys of polymeric materials.

4.1.1.2 Occupational exposure

The production of PTBBA in the EU was ceased in the year 2006. Presently there are three importers in the EU market.

The following occupational exposure limits (OEL) and short term exposure levels (STEL) apply in the EU (Ariel, 2006):

Country	OEL	STEL
The Netherlands	2 mg/m^3 (inhalable dust)	-
Germany, Swiss	2 mg/m^3 (inhalable dust)	4 mg/m^3 (inhalable dust)

The assessment of inhalation exposure is mainly based on measured exposure levels from which – if possible – 90th percentiles are derived as representing reasonable worst case situations.

Scenarios are clustered as far as possible to make the description transparent. If quantitative exposure data is not available, model estimates are taken.

Beside inhalation exposure, dermal exposure is assessed for each scenario. Two terms can be used to describe dermal exposure:

Potential dermal exposure is an estimate of the amount of a substance landing on the outside of work wear and on the exposed skin.

Actual dermal exposure is an estimate of the amount of a substance actually reaching the skin.

Within the framework of existing substances there is an agreement between the EU-member states, to assess - as a rule - dermal exposure as exposure to hands and parts of the forearms. In this, the main difference between both terms – potential and actual - is the protection of hands and forearms by work wear and – more important – the protection by gloves. Within this exposure assessment, the exposure reducing effect achievable by gloves is only considered if information is provided indicating that, for a certain scenario, gloves are a widely accepted protective measure and that the gloves are fundamentally suitable for protection against the substance under consideration. As a measure for the latter, tests according to DIN EN 374 are taken as a criterion. For most downstream uses it is commonly known that gloves are not generally worn. In these cases, dermal exposure is assessed as actual dermal exposure for the unprotected worker. Since quantitative information on dermal exposure is often not available, the EASE model is usually used for assessing dermal exposure.

The following scenarios are regarded to be relevant for occupational exposure:

Scenario 1: Further processing of PTBBA (4.1.1.2.1)
Scenario 2: Production of alkyd resins in the polymer industry (4.1.1.2.2)

Due to the physico-chemical properties of the substance (solid at room temperature) inhalation exposure to vapour (vapour pressure: 0.057 Pa) is assumed to be negligible (Clariant, 2003). Inhalation exposure to dust at the workplace during handling the substance must be taken into consideration.

In alkyd resins most of the PTBBA reacts with the hydroxyl groups. From information from industry it is estimated that less than 0.1 % PTBBA is left unreacted in the resin solution and hardened resin (Interorgana, 2001). Due to this low concentration in the resin it is assumed that the downstream uses of resins are not relevant for this exposure assessment.

4.1.1.2.1 Further processing of PTBBA

Inhalation exposure

In Scenario 1 the production of PTBBA-salts and its further use as a stabiliser for PVC and the PTBBA use as a chemical intermediate (production of pigments, anaesthetics etc.) are clustered.

Production of PTBBA salts and further use as stabiliser for PVC

PTBBA salts of commercial importance include those of aluminium, zinc, sodium, cadmium and strontium.

Various organic acids, including PTBBA, are introduced in a closed vessel and reacted with mixed metal oxides or hydroxides in a non-aqueous solvent to form the respective salts. The final product is liquid. Solid PTBBA has low dust characteristics and is loaded into the reactor, generally from a silo through a conveyor tube or sometimes directly from bags. The reactor is under depression during loading or equipped with an aspiration cap. This loading step takes place once during each batch processing. This results in an exposure of maximum 1 hour during a full day of production in the case of loading from a silo or from big bags. Most plants process PTBBA 220 working days/year. The number of workers is limited, as the loading operation is normally conducted by a single operator (ESPA, 2007).

PTBBA salts are used as stabilisers in certain PVC types and blends (Interorgana, 1999). According to industry, the share of the metal salts in the formulation is up to 1.5 % (see chapter 2.2.2.3.). In final products of these PVC types and blends the content of the PTBBA salts is < 0.2 %. Currently no data on migration of the PTBBA salts out of the PVC matrix are available. But it can be assumed that the PTBBA salts might have a very low tendency for migration in the PVC matrix and exposure is most likely not relevant (Clariant, 2002).

During the manufacturing of PVC types and blends exposure to PTBBA salts is possible. A limited number of experienced workers wearing gloves and goggles and using exhaust ventilation are potentially exposed at that customer's site (Clariant, 2002).

PTBBA use as an intermediate

Esters of PTBBA – mostly methyl and vinyl esters – are important precursors of UV sun screens. These esters are prepared from PTBBA by esterification. The esters may contain the starting material as an impurity (< 0.1 %, Clariant, 2002). Alkanolamine salts of PTBBA are used as corrosion inhibitors and are components in cutting fluids.

During the manufacturing of PTBBA esters occupational exposure is possible during the handling of PTBBA powder. Appropriate personal protective equipment (PPE) is worn by the workers and the exposure time is limited (Clariant, 2002).

Exposure associated with transporting the chemical could result from loading, unloading and drumming operations. For the large-scale chemical industry high standards of control at the workplace are assumed to be practiced even if the containment is breached, e.g. during bagging, cleaning, maintenance, repair works and taking of samples. Inhalation exposure in other fields is normally minimized by technical equipment (e.g. special designed filling stations, local exhaust ventilation LEV).

Measured data

PTBBA concentration in air is monitored in PTBBA salt producing plants. Industry has measured the concentration of PTBBA in air during the loading phase by personal and/or static monitoring. The dust was collected during 1 hour with pump and filter system. Two plants reported below 0.01 mg/m^3 of PTBBA (analysis of the collected dust with chromatography). The third plant reported 0.05 mg/m^3 with a non specific analytical method. Therefore, 0.05 mg/m^3 can be regarded as a real worst case for the concentration of PTBBA in air during the loading step. Considering that the process are the same for all the plants run by ESPA (European Stabilisers Producers Association) members, it is justified to consider those data as representative for the whole sector (ESPA, 2007).

Information provided by industry for the use of PTBBA as chemical intermediate is confidential and summarised as follows:

Workplace air measurements of PTBBA dust at the production of PTBB-ester in 2001 were up to 1.31 mg/m^3 (7 samples).

Modelled data

EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for the further processing of PTBBA:

Input parameters: T = 20 °C, exposure type is dust, low dust technique, LEV present

Level of exposure: 0 - 1 mg/m^3

Two granulometric measurements revealed that 0.1 % of the product comprise a particle size below 300 µm and 0.7 % below 100 µm, respectively. Therefore the category "low dust techniques" is chosen.

Summary/statement of the exposure level

Inhalation exposure has to be assessed for the further processing of PTBBA in fields with high levels of protection, e.g. in the large-scale chemical industry.

For the assessment of health risks from daily inhalation exposure to PTBBA during the production of PTBBA salts an 8 h time weighed average concentration (8 h TWA) of 0.05 mg/m^3 (workplace measurements) should be taken to represent a reasonable worst case situation. It is to be assumed that the substance is processed daily. Consequently, the duration and the frequency of exposure to PTBBA are assumed to be daily and for one hour per shift.

For the assessment of health risks from daily inhalation exposure to PTBBA during the use of PTBBA as a chemical intermediate an 8 h time weighed average concentration (8 h TWA) of 1.0 mg/m^3 (EASE estimation) should be taken to represent a reasonable worst case situation. It is to be assumed that the substance is processed daily. Consequently, the duration and the frequency of exposure to PTBBA are assumed to be daily and for the entire length of shift.

Dermal exposure

At the production of PTBBA salts and the use of PTBBA as a chemical intermediate dermal exposure could occur during activities like filling, dosing, sampling, cleaning, maintenance and repair work.

Modelled data

For the unprotected worker, according to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, direct handling, intermittent
Level of exposure: 0.1 – 1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (equivalent of one hand) the model yields an exposure level of 42 - 420 mg/person/day.

For assessing actual dermal exposure levels, it has to be considered that the substance is processed primarily in closed systems and that the use of PPE (here gloves and eye protection) is highly accepted in the large-scale chemical industry. The extent of protection by PPE (here gloves) depends inter alia on the suitability of the recommended material with regard the permeation properties of the substance. For the handling of powdery substances, as a rule, the suitability of the gloves can be assumed. As a rough estimation, a protection efficiency of 90 % achieved by suitable gloves is taken. The suitability of the used gloves under real working conditions is considered in the assumption of 90 %-protection. However, the protection efficiency might be higher, but quantification is not possible. As a result, dermal exposure is calculated to 4.2 – 42 mg/person/day. The upper value is regarded as representing the reasonable worst case situation.

Summary/statement of the exposure level

For assessing the health risks from daily dermal exposure in the area of further processing (scenario 1), an exposure level of 42 mg/person/day should be taken. This exposure assessment is based on the information, that suitable gloves are worn and takes into account the possible dermal exposure under actual workplace conditions.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.2 Production of alkyd resins in polymer industry

Inhalation exposure

PTBAA is used as a modifier (chain stop agent) in the polymerisation of alkyd resin to improve paints and lacquers characteristics (PTBBA quantity: 1350 t/a). Alkyd resins are used in a large number of applications, particularly in the surface coating industry (paints, enamels, lacquers, and varnishes).

Alkyd resins are manufactures in large reactors. The manufacture of resins involves the use of natural oil or a fatty acid, a polyol such as pentaerythritol and a dicarboxylic acid or acid anhydrid. PTBBA is dosed via manhole to the reactor. At the polymersiation step PTBBA reacts with the alkyd monomer (Jones, 2003). After a period ranging from 8 to 20 h, the resin is downloaded into a thinning vessel where more solvents are added and finally pressed through filters. The resins are either stored in drums or in large tanks.

According to industry PTBBA is added into the mixture in a share of 1-10 % (Interorgana, 2003). Most of the PTBBA reacts with hydroxyl groups in the resin. According to limited information from customers it is estimated that less than 0.1 % PTBBA is left unreacted in the resin solution or hardened resin (Interorgana, 2002).

Due to this low concentration in the resin it is assumed that the downstream uses of resins are not relevant for this exposure assessment.

During charging of solid PTBBA in the reactor vessels (handling of bags) exposure to PTBBA is possible. The exposure time varies between 5 to 30 minutes (emptying 25 kg bags, or big bags). Workers are protected by appropriate PPE and by vacuum supported filling of vessels (Clariant, 2002, DSM, 2007).

Measured data

No workplace measurements are available.

Modelled data

EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for the production and further processing of PTBAA:

Input parameters: T = 20 °C, exposure type is dust, low dust technique, LEV present

Level of exposure: 0 - 1 mg/m^3

The category "low dust techniques" is chosen due to the high amount of particle sizes greater than 100 µm (99.3 %). According to informationen from the industry dosing of PTBBA into the reactor lasted approx. 30 minutes. Considering the reduced exposure duration of 30 minutes the resulting exposure level is 0.0625 mg/m^3.

Summary/statement of the exposure level

Inhalation exposure has to be assessed for the charging of solid PTBBA during the production of alkyd resins.

For the assessment of health risks of daily inhalation exposure to an 8 h time weighed average concentration (8 h TWA) of 0.0625 mg/m^3 (EASE estimation) should be taken to represent a reasonable worst case situation.

It is to be assumed that PTBBA is used daily. Consequently, the duration and the frequency of exposure to PTBBA are assumed to be daily and for 30 minutes.

Dermal exposure

For the charging of solid PTBBA during the production of alkyd resins (polymer industry) it is to be assumed that protective gloves are regularly worn.

Modelled data

For the unprotected worker, according to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, direct handling, intermittent
Level of exposure: 0.1 – 1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (palms of hands) the model yields an exposure level of 42 - 420 mg/person/day.

Summary/statement of the exposure level

For assessing actual dermal exposure levels, it has to be considered that the substance is further processed primarily in closed systems and that the use of PPE (here gloves and eye protection) is highly accepted in the polymers industry. The extent of protection by PPE (here gloves) depends inter alia on the suitability of the recommended material with regard the permeation properties of the substance. For the handling of powdery substances, as a rule, the suitability of the gloves can be assumed. As a rough estimation, a protection efficiency of 90 % achieved by suitable gloves is taken. As a result, dermal exposure is calculated to 4.2 – 42 mg/person/day. The upper value is regarded as representing the reasonable worst case situation.

For assessing the health risks from daily dermal exposure in the area of alkyd resin production (scenario 2), an exposure level of 42 mg/person/day should be taken. This exposure assessment is based on the information provided by the producers and importers, that suitable gloves are worn and takes into account the possible dermal exposure under actual workplace conditions.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.3 Summary of occupational exposure

Based on the available information, 43 % of the PTBBA are used in the manufacturing of alkyd resins. Due to the low concentration of PTBBA (< 0.1 %) in the resin it is assumed that the downstream uses of resins are not relevant for this assessment. The other 53 % are further processed to PTBBA metal salts or esters and the last 4 % are used as an intermediate for the production of pigments, anaestethics etc.

For occupational exposure there are two scenarios relevant:

- Further processing of PTBBA

- Production of alkyd resins in the polymer industry

The inhalation and dermal exposure levels are given in table 4.1.

For the large scale chemical industry, it is assumed that the further processing of PTBBA is mainly performed in closed systems. This is also true for the production of alkyd resins in the polymer industry. Exposure occurs if the systems are breached for certain acitvities, e.g. bagging, charging, maintenance. Exposure is possible during the handling of the powdery substance. It is considered that PTBBA is sold as a low dust product (particle size: only 0.7 % below 100 µm) which leads to reduced inhalation exposure.

Dermal exposure was assessed in consideration of a high level of protection realised in the chemical industry, and the polymer industry and with the assumption that suitable gloves are regularly worn. As concerning dermal exposure, for the handling of powdery substances, as a rule, the suitability of the gloves can be presupposed. A protection efficiency of 90 % is assumed.

Table 4.1 Conclusions of the occupational exposure assessment

Scenario	Activity	Frequence Days/year	Duration Hours/day	Inhalation				Dermal			
				Full shift				Full shift			
				Reasonable worst case		Typical concentration		Reasonable worst case		Typical concentration	
				Unit	Method	Unit	Method	Unit	Method	Unit	Method
1 a) Production of PTBBA salts	loading, filling, maintenance	daily	1 h	0.05 mg/m³	Measurement	-	-	42 mg/p/day	EASE (with gloves)	-	-
1 b) PTBBA used as a chemical intermediate		daily	8 h	1.0 mg/m³	EASE	-	-				
2) Production of alkyd resins in the polymer industry	charging, dosing	daily	30 min	0.0625 mg/m³	EASE	-	-	42 mg/p/day	EASE (with gloves)	-	-

4.1.1.3 Consumer exposure

In the Swedish product register, and the BfR product database (2001 referred to as BgVV database), no consumer products were found that contain 4-tert-butylbenzoic acid (PTBBA).

According to updated information of the Swiss Product Register (December 2006) the one product which was assigned to the consumer use previously (September 2002) is not any more available.

It has been found in literature that exposure of humans may occur by contact with sex toys of polymeric materials as soft vinyl or thermoplastic rubber. Nilsson et al. (2006) measured concentrations of PTBBA among other chemical substances in detectable amounts.

Screening analyses by GC/MS from dichloromethane extracts in samples of a transparent bra and an artificial vagina resulted in values of 0.3 g/kg sample. In migration analyses amounts of 20 – 100 µg per dm^2 were determined for artificial vagina using sweat with a pH level of 6.5. An estimation of dermal exposure did not take place for PTBBA.

According to the assumptions for exposure estimation of other chemicals, the area of exposure for artificial vagina accounts for 150 cm^2 and time of exposure (worst case) is 1 hour/day. The external dermal exposure can be calculated by the following equation (TGD, 2003) and account for 2.5 µg/kg bw per day.

$Exp_{external, derm} = (M \times A \times H) / bw$

M: migrated amount of substance (µg/dm^2 per 1 hour)
A: exposed skin area (cm^2)
H: time of exposure per day (hour)
bw: 60 kg

4.1.1.3.1 Summary of consumer exposure

There is no information for the use of consumer products containing PTBBA. The BfR-product database and other available European databases do not give evidence for use of PTBBA in consumer products.

According to Nilsson et al. (2006) exposure may occur by contact with sex toys. Data to the content of PTBBA in transparent bra and artificial vagina are given as well as data to migration from artificial vagina. But there are no data to dermal exposure. Taking the above mentioned worst case assumptions an external dermal exposure can amount up to 2.5 µg/kg bw per day.

4.1.1.4 Humans exposed via the environment

The indirect exposure of humans to PTBBA via the environment is assessed at two levels:

(1) the exposure to average background concentrations on a regional scale; and

(2) the exposure to potentially higher concentrations which may exist near point sources such as industrial production and processing sites on a local scale.

While the local assessment represents a worst-case scenario, in which all food products are assumed to come from the vicinity of a point source, the regional assessment gives an indication of the potential average exposure of the inhabitants of a region under the assumption that all food products are taken from the regional model environment.

The estimated daily human intake from indirect exposure on a local and regional scale is presented in Table 4.2. The estimates are based on calculations performed with EUSES 2.0.3 (confidential Appendix) and according to the specifications of the TGD. LogKow and water solubility at pH 5 and pH 7, which have been used in the respective EUSES studies, are presented in Chapter 3.1.3.2. As all other industrial sites are estimated to cause no or negligible local exposure, only the local scenario representing flexible PVC compounding and converting sites is included.

The local indirect exposure in the environment with pH 5 causes total daily intake of $3.8\ 10^{-4}$ mg kg^{-1} d^{-1} whereas intake at pH 7 is $2.25 * 10^{-4}$ mg kg^{-1} d^{-1} in total. As the realistic worst case estimate, exposure at pH 5 is presented in detail below. For daily intake in regional scenario, the intake at pH 5 is presented in detail for the reasons of comparability, although total regional intake at pH 7 is slightly higher ($5.99 * 10^{-6}$ mg kg^{-1} d^{-1} in total).

Monitoring data for PTBBA in the different intake media (drinking water, fish, leaf and root crops, meat, milk and air) are not available, so that exposure data derived from modeling cannot be compared to actual exposure data.

Table 4.2 Estimated human intake of PTBBA [mg/kg bw/d] via the different intake media and percentage of total uptake.

Scenario	Local		Regional	
	Use as stabilizer in PVC - compounding and conversion site			
Intake media	**mg/kg bw/d**	**%**	**mg/kg bw/d**	**%**
Drinking water	$7.3 \cdot 10^{-5}$	19.1	$3.2 \cdot 10^{-6}$	55.3
Fish	$4.2 \cdot 10^{-5}$	11	$1.8 \cdot 10^{-6}$	31.8
Leaf crops	$2.6 \cdot 10^{-4}$	68.6	$6.0 \cdot 10^{-7}$	10.4
Root crops	$1.3 \cdot 10^{-6}$	0.3	$1.5 \cdot 10^{-7}$	2.6
Meat	$6.1 \cdot 10^{-8}$	0.02	$4.4 \cdot 10^{-10}$	$8 \cdot 10^{-5}$
Milk	$7.5 \cdot 10^{-8}$	0.02	$5.4 \cdot 10^{-10}$	$9 \cdot 10^{-5}$
Air	$3.9 \cdot 10^{-6}$	1	$7.2 \cdot 10^{-9}$	0.001
Total intake	$3.8 \cdot 10^{-4}$	100	$5.8 \cdot 10^{-6}$	100

4.1.1.4.1 Exposure via air

An intake of PTBBA via air is considered as negligible.

4.1.1.4.2 Exposure via food and water

Calculations for the scenario "Use as stabilizer in PVC" resulted in a total daily intake of 0.00038 mg/kg bw/d at the local level. For the regional scenario a total daily intake of $5.8 \cdot 10^{-6}$ mg/kg bw/d was calculated.

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

4.1.2.1 Toxicokinetics, metabolism and distribution

Data on toxicokinetics, metabolism and distribution of 4-tert-butylbenzoic acid after oral, dermal and inhalative uptake in animals and humans are not available. Therefore, an estimation of absorption based on physico-chemical data and on results of toxicological investigations is performed.

From physico-chemical properties (water solubility (47.1 mg/l), molecular weight (178.23 g/mol) and the octanol-water partition coefficient log Pow of 3.4) the substance can be assumed to have a probably good oral bioavailability. However, due to the pKa of 4.36, only small amounts of the substance may be present in the non-ionized form at the pH values present in small intestine (pH 4-6 according to TGD). This makes complete absorption from the small intestine unlikely. Toxic effects, which can be observed after acute and subacute oral application of the substance (a NOAEL cannot be derived; a LOAEL exists), are indicative of gastrointestinal absorption, but quantification is not possible. Therefore, oral absorption is assumed to be 100 % (default-value).

Due to its molecular weight below 500 and a log Pow value between –1 and 4, 100 % dermal absorption can be assumed according to TGD. This assessment is further supported by calculations according to Potts and Guy (1992). Toxic effects, which can be observed after acute and repeated dermal application of PTBBA to the skin of rats are indicative of dermal absorption. Quantification is not possible. Therefore, dermal absorption is assumed to be 100 % (default-value).

Based on the low vapour pressure of 0.057 Pa at 20°C and its physical state (crystalline solid at room temperature), inhalative uptake is possible if exposure to particle dust (where particle size is small enough) is given. Toxic effects which could be observed after acute and repeated exposure of rats towards particle dusts of 4-tert-butylbenzoic acid (maximal median mass diameter: 5.5 µm) are indicative of inhalative uptake. Quantification of inhalative uptake of PTBBA is not possible. Therefore, absorption via inhalation is assumed to be 100 % (default value).

4.1.2.1.1 Studies in animals

Oral

After 5-day oral administration of p-tert-butylbenzaldehyde to rats, (doses of 12.5 and 50 mg/kg bw/d), p-tert-butylbenzoic acid was identified as metabolite in the urine 24 hours after the last administration, probably as a glucuronide conjugate. The isolation of further unidentified metabolites indicated that a subordinate secondary biotransformation pathway (oxidation of the tert-butyl-moiety) could occur (Anonymous 1982).

4.1.2.1.2 Studies in humans

No data available.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

There are no data available on the toxicokinetics, metabolism and distribution of 4-tert-butylbenzoic acid after inhalation, oral and dermal exposure in animals or humans. Taking into account the physico-chemical properties of PTBBA (molecular weight 178 g/mol, water solubility of 47.1 mg/l, log Pow of 3.4, and vapour pressure of 0.057 Pa), the state of ionisation and available toxicological information an extent of absorption of 100% via inhalation, dermal and oral exposure will be assumed (default).

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

In vivo studies

Inhalation

Groups of 6 male and 6 female Fischer rats were exposed to PTBBA dust (purity 99.4%) at concentrations of 0.0, 0.495 , 0.668, 0.958 or 1.802 mg/l for 4 hours. The MMAD was in the range of 4.0-5.5 micrometer. At the highest concentration of 1.802 mg/l 2/6 males and 1/6 females died. This indicates that the LC50 is > 1.802 mg dust/l. However, other major toxicological effects were seen at all concentrations tested and a No-Effect-Level for a single four hour exposure could not be determined. At the lowest concentration of 0.495 mg/l effects on testes, in spinal cord and on rate of body weight gain were noted. Testicular effects were characterised among others by decreased sperm counts and microscopic lesions including reduction of tubular multinucleated cells. The forelimb neuropathy was described microscopically as multifocal poliomyelopathy. Decreased rate of body weight gain was observed in both sexes on days 4 and 14 exposed to all dose levels of PTBBA (Darmer et al., 1982; Darmer et al., 1984; Lu et al., 1987).

Dermal

The acute single dose percutaneous LD50 value of PTBBA (no data on purity) as a 30% solution in DMSO (w/v) was found to be approximately 300 mg/kg in Carworth Farm E strain (CFE) rats in a study using 2 males and 2 females each at dose levels of 75, 150, 300, and 900 mg/kg bw. After application of 75 mg/kg none of the rats died, after application of 150 mg/kg 0/2 males and 1/2 females died on day 2, after application of 300 mg/kg 2/2 males and 0/2 females died within 4 days, after application of 900 mg/kg all rats died within 4 days. No further information is given (Shell Research Ltd. London, unpublished report 1975).

In studies with New Zealand White rabbits, however, a dermal LD50 value of > 900 mg/kg bw for a 30% solution in DMSO (w/v), and of > 2000 mg/kg bw for the dry powder were determined. The acute single dose percutaneous LD50 value of 4-tert- butylbenzoic acid (no data on purity) as a 30% w/v solution in DMSO was found to be greater than 900 mg/kg, the maximum volume of the most concentrated solution that could be used. The LD50 value of the dry powder was found to be greater than 2000 mg/kg in rabbits. No pathological lesions were found in the tissues of the rabbits exposed to the powdered substance. No further information is given (Shell Research Ltd. London, unpublished report 1975).

Oral

An oral LD50 of 735 (642-8457) mg/kg bw was found in a study with albino Carworth Farm rats using 4-tert-butylbenzoic acid (no data on purity) formulated as a 10% (w/v) solution in a mixture of acetone and dimethylsulphoxide (3:7, w/v): Doses of 500, 630, 800, 1000 and 2000 mg/kg bw were administered to groups of normally 4 female and 4 male rats each. Rats given twice the LD50 dose went into a prone position 60 min after dosing. There was excessive salivation and upright flicking of the tail was seen. The hind limbs became extended. Convulsions could be produced by tapping the bench alongside the rat. Finally, the rats took up a lateral position with the hind limbs retracted; respiratory gasping preceded death which appeared to be due to respiratory failure. The final mortality was recorded on day 18 after dosing and resulted in 0/5 males after administration of 500 mg/kg, 1/5 males after 630 mg/kg, 4/4 males after 800 mg/kg , and 3/4 males after 1000 mg/kg. Mortality after administration of 2000 mg/kg to males and mortality of the females is not reported. Some 36 rats, young males and females, dying or sacrificed 18-24 days after single oral doses of 500-2000 mg/kg bw were subjected to necropsy. All animals dying from the exposure, except one female rat, showed only the usual gross signs of acute poisoning; congestion of the viscera and the venous circulation, which was confirmed histologically. In the gut the signs of injury were limited to congestion of the mucosa and post-mortem degeneration. A solitary female rat dying 48 hours after treatment presented evidence of slight toxic degeneration of the parenchyma in the outer zones of the lobules at the liver together with congestion of the sinusoids. However, when 18 male survivors were examined 18 and 24 days after treatment, damage to the male gonad became evident. Testicular atrophy was produced in 4/5 male rats exposed to a single dose of 500 mg/kg bw No female rats were pregnant although cohabiting with male rats and 8/10 male survivors had demonstrable bilateral atrophy of the testes. The testes were shrunken, their parenchyma was pinkish and felt like "bags of jelly". These organs weighted 50-60% of the normal weight. The ovaries of the surviving females were of normal appearance and presented no histological evidence of abnormal oogenesis. In summary, no specific signs of structural injury were found in rats dying after lethal oral doses of the material but in the male survivors, the testes presented extensive bilateral atrophy due to a degeneration of the generative cells in the seminiferous tubules (Hunter et al., 1965).

In an acute oral toxicity study with Sprague-Dawley albino rats using the up and down procedure, oral LD50 values of 720 (540-980) mg/kg bw for male and of < 720 mg/kg for female rats were detected after oral gavage of 4-tert-butylbenzoic acid (purity > 99%) as a 7.5% (w/v) suspension in 1 molar aqueous NaCl solution. One male animal was administered an initial dose of 700 mg/kg bw. Subsequent dose levels either decreased or increased by a progression of approximately 1.3 based upon the 24-hours mortality result of the previous level. Once the initial point of reversal in the survival rate had been determined, four additional levels for each group were dosed using the above procedure. Additional testing included: 1) Six females treated at the male LD50 value and 2) One male at each of 2 dose levels bracketing the LD50 value but using 40% (w/v) suspensions of the test material in water. These procedures resulted in 0/1 male rats dying after administration of 500 mg/kg, 1/3 males dying after administration of 700 mg/kg and 2/2 males dying after administration of 900 mg/kg of the 7.5% suspension in aqueous NaCl solution; six out of six females died after administration of 700 mg/kg of this suspension. Two male animals dosed with 500 mg/kg and with 900 mg/kg of the 40% aqueous suspension survived. Each animal was observed for clinical signs and mortality at 0.5, 2 and 4 hours following test material administration. The animals were observed daily thereafter for 7 days for clinical signs and mortality. Clinical signs seen during the study included hypoactivity, ataxia, thin appearance, hunched posture, impaired use of front limbs, yellow-stained anal area, tremors, prostration, excess salivation, hypothermia to the touch, bradypnoea, absence of pain reflex, spasticity, mydriasis, flaccidity, respiratory congestion, and death. One animal also exhibited cyanosis, an absence of pain reflex, and a reddish material on its face and front paws. All deaths occurred within 24 hours after dosing. At study termination, surviving animals were euthanatised. All animals, whether dying on study or euthanatised, were subject to a gross necropsy examination, and all abnormalities were recorded. This resulted in the following observations: clear fluid stomach content, stomach enlarged, glandular mucosa diffusely red, tan to dark tar mucoid material in the small intestine, red perinasal discharge, right submandibular lymph node enlarged (Procter & Gamble Comp., unpublished report 1986a).

In an additional test, 10 male Sprague-Dawley albino rats were dosed by gavage with 720 mg/kg bw of 4-tert-butylbenzoic acid (purity > 99%) as a suspension in 1molar aqueous NaCl solution. All animals were observed for mortality at 0.5, 2, and 4 hours following test material administration and daily thereafter for 14 days. Body weights were taken before testing, just prior to test material administration, at 7 and 14 days of the study, and at death. Clinical signs seen during the study included hypoactivity, ataxia, bradypnoea, yellow-stained abdomen, impaired use of front limbs, and death. Two out of the ten male rats died within 2 hours following test material administration. All but one surviving animal had returned to normal by day 6 of the study. All animals were given a complete gross necropsy examination and all abnormalities were recorded. The liver, kidneys, and testes were removed and weighed from all animals that survived the 14-days observation period as well as from any animal that was sacrificed in extremis. Macroscopic observation detected small testes in one animal, microscopic observation detected hypospermatogenesis of the testes. This condition existed in all animals treated. Even though the cells appeared normal, these animals had fewer spermatogenic cells in the semiferous tubules than those of the control animals. Mean absolute and relative testes weight were significantly lower in animals treated, and these lower values correlated well with the microscopic findings of hypospermatogenesis of the testes that were observed in these animals (Procter & Gamble Comp., unpublished report 1986b).

A further test at the approximate LD50 was performed dosing 10 male Sprague-Dawley albino rats with 700 mg/kg bw of 4-tert-butylbenzoic acid (purity > 99%) as a suspension in acetone and dimethylsulphoxide (3:7, w/v). All animals were observed for mortality at 0.5, 2, and 4 hours following test material administration and daily thereafter for 14 days. Body weights were taken before testing, just prior to test material administration, at 7 and 14 days of the study, and at death. Clinical signs seen during the study included hypoactivity, ataxia, bradypnoea, no pain reflex, possible respiratory congestion, prostration, yellow-stained anal area, lacrimation, hypothermic to touch, and death. Seven of the 10 rats died within 1 day following test material administration. All surviving animals had returned to normal by day 5 of the study. All animals were given a complete gross necropsy examination and all abnormalities were recorded. The liver, kidneys, and testes were removed and weighed from all animals that survived the 14-days observation period as well as from any animal that was sacrificed in extremis. Macroscopic observation detected small testes in one animal, microscopic observation detected hypospermatogenesis of the testes. This condition existed in all animals treated. Even though the cells appeared normal, these animals had fewer spermatogenic cells in the semiferous tubules than those of the control animals. Mean absolute and relative testes weight were significantly lower in animals treated, and these lower values correlated well with the microscopic findings of hypospermatogenesis of the testis that were observed in these animals (Procter & Gamble Comp., unpublished report 1986b).

An approximate oral LD50 of > 550 but < 800 mg/kg bw resulted when doses of 550 and of 800 mg/kg were administered to 2 female Long-Evans rats per dose intragastically as a suspension of 4-tert-butylbenzoic acid, containing 5% of the m-compound (3-tert-butylbenzoic acid, Shell production grade) in a mixture of ethanol, water, and gum acacia. After administration of 550 mg/kg both rats survived, after administration of 800 mg/kg both rats died on the day of dosing. Marked depression of activity was noted, one rat given 800 mg/kg could be disturbed only by pinching the paws or tail. Autopsy of the rats dosed with 800 mg/kg showed greatly irritated lungs in both, and hemorrhages of the rugae of the stomach in one rat (Shell Development Company, unpublished report 1950).

An oral LD50 of 568 mg/kg bw resulted in a study with Swiss inbred white mice tested by intragastic administration of an aqueous suspension of 4-tert-butylbenzoic acid, containing 5% of the m-compound (Shell production grade, no data on purity) in gum acacia. Doses of 350, 400, 550, 600, 650, 700, and 800 mg/kg bw were given to 10 mice each resulting in the following mortalities: after administration of 350 mg/kg 1/10 mice died on day 2; after administration of 400 mg/kg 4/10, after 550, 600, and 650 mg/kg 5/10 each, after 700 mg/kg 7/10, and after 800 mg/kg all mice died within 24 hours. The mice were mildly depressed within 1/3 hours after dosing. Within an hour, signs of muscular distress, marked incoordination and the Straub tail effect (spinal cord excitant) were present. At 5 hours a paralysis of the forelegs was evident in two thirds of the mice. In 3 of these, response of the tail and paws to painful stimuli was depressed or absent, but recovery occasionally followed even this deep depression. The pathologic changes noted in the 22 mice autopsied included signs off lung irritation, hemorrhage of the lungs, increased pigmentation of the liver, denuding of the epithelium of the intestines, and hyperemia of the intestines (Shell Development Company, unpublished report 1950).

In vitro studies

[click here to insert text]

4.1.2.2.2 Studies in humans

In vivo studies

Inhalation

No data available

Dermal

No data available

Oral

No data available

4.1.2.2.3 Summary of acute toxicity

4.1.2.3 Human data on acute toxicity of 4-tert-butylbenzoic acid are not available. In studies with rats, oral LD50 values of > 550 mg/kg and < 800 mg/kg bw were detected with females being slightly more sensitive than males (Hunter et al., 1965; Procter & Gamble Comp. 1986; Shell Comp. 1950). Testicular atrophy was produced in male rats exposed to a single dose of 500 mg/kg, and degeneration of the generative cells in the seminiferous tubules was observed. The ovaries of surviving female rats were of normal appearance and presented no histological evidence of abnormal oogenesis (Hunter et al., 1965). The oral LD50 for mice was determined at 568 mg/kg bw (Shell Comp. 1950). An inhalation LC50 was not determined but exposure of rats to 1.802 mg dust/l/4 hours resulted in death in 2/6 male and 1/6 female rats. This indicates an LC 50 of > 1.8 mg/l. In these experiments testicular and CNS changes and changes in body weight were noted at the lowest concentration tested at 0.495 mg/l (Darmer et al., 1982; Darmer et al., 1984; Lu et al., 1987). The assessment of acute dermal toxicity is difficult, because the available data demonstrated great species differences (Shell Research Ltd. London, unpublished report 1975). In rats, a dermal LD50 of approximately 300 mg/kg resulted when a 30% substance solution in DMSO was tested. In rabbits the dermal LD50 was found to be > 2000 mg/kg when the dry powder was applied. Based on the above data, 4-tert-butylbenzoic acid is to be classified "Xn, harmful" and labelled with "R 22, Harmful if swallowed". The TC C&L in September 2007 agreed that for acute toxicity the available LC50 for inhalation and the LD50 for dermal application were not sufficient for classification.Irritation

4.1.2.3.1 Skin

Studies in animals

No signs of skin irritation were observed in a Draize skin irritation test with one male and one female albino rabbits which were depilated over the skin area to be exposed for 8 hours to solid 4-tert-butylbenzoic acid, containing 5% of the m-compound (3-tert-butylbenzoic acid, Shell production grade) and to a mixture of the substance with alcohol and mineral oil under a confining rubber dam. Applications of 800 mg/kg bw in the solid and 300 mg/kg bw in the alcohol-mineral oil suspension were made. Neither preparation caused systemic or skin changes (Shell Development Company, unpublished report 1950).

In a test performed according to EU test guideline B4, no signs of skin irritation resulted after a 4-hours single application of 500 mg of 4-tert-butylbenzoic acid (no data on purity) moistened with water. The substance was applied to a clipped area of 6 New Zealand albino rabbits and was held in contact with the skin for 4 hours by a semi-occlusive dressing. The cutaneous reactions were observed 1, 24, 48, and 72 hours after the removal of the dressing. No cutaneous reaction was detected (Hoechst AG, unpublished report 1988).

Studies in humans

No data available

4.1.2.3.2 Eye

Studies in animals

Only signs reported as "minimal irritation" were seen in a Draize eye irritation test with one male and one female albino rabbit which were given 100 mg of solid 4-tert-butylbenzoic acid, containing 5% of the m-compound (3-tert-butylbenzoic acid, Shell production grade, no data on purity) into the conjunctival sac of the eye. "Minimal irritation" was noted in one case and none in the other (Shell Development Company, unpublished report 1950).

Mild eye irritation reversible within 3 days resulted in a study according to EU test guideline B5: A single introduction of 100 mg of undiluted 4-tert-butylbenzoic acid (no data on purity) was performed into the left eye of 6 New Zealand albino rabbits. The ocular reactions were observed 1, 24, 48, and 72 hours after the introduction in order to observe their reversibility or their irreversibility. One hour after instillation of the test substance, moderate conjunctival reactions (redness and chemosis maximum grade 2) and slight discharge were observed in all animals. After 24 hours, the conjunctival reactions regressed and were slight in all animals and corneal opacity grade 1 and grade 2 was noted in 2 animals. After 48 hours, only slight conjunctival lesions persisted in 1 animal; after 72 hours no ocular reaction was noted (Hoechst AG, unpublished report 1988).

Studies in humans

No data available

4.1.2.3.3 Respiratory tract

No data available.

4.1.2.3.4 Summary of irritation

Human data on skin or eye irritation caused by 4-tert-butylbenzoic acid are not available. In Draize tests with rabbits the substance did not cause any signs of irritation to the skin (Hoechst AG, unpublished report 1988) and only mild reversible irritation to the eyes of rabbits (Hoechst AG, unpublished report 1988). Based on these data, the substance is not to be classified as irritant or corrosive, no labelling with R-phases is warranted.

4.1.2.4 Corrosivity

4-tert-Butylbenzoic acid has proven to cause no skin irritation in rabbits (cf. 4.1.2.3.1). Mild eye irritation in rabbits was reversible (cf. 4.1.2.3.2). Thus, PTBBA has no corrosive properties.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

In a Maximization Test (Magnusson Kligman Test) p-tert-butyl benzoic acid with a purity of 99.6% was tested in albino guinea pigs (Himalayan spotted). Ten test and 5 control animals were used. For intradermal injection a 25% substance concentration, for dermal induction a 50% concentration and for challenge a 25% concentration was used. The vehicle was PEG 300. Slight irritation was noted after dermal induction. None of the test and control animals showed skin reactions after the challenge treatment (Clariant, 2003).

4.1.2.5.2 Studies in humans

Skin

No data available

4.1.2.5.3 Summary of sensitisation

In a Maximization Test (Magnusson Kligman Test) guinea pigs showed no skin reactions after the challenge treatment. Human data on skin sensitization are not available for 4-tert-butylbenzoic acid. At present, no labeling for skin sensitizing properties is warranted.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

In vivo studies

Inhalation

In a dose-range finding study (HRC, 1994) three groups of Sprague Dawley rats (3 males and 3 females/group) were exposed in a snout-only exposure to 4-tert-butylbenzoic acid for 6 hours on 5 consecutive days. The target concentrations were 1.5, 5.0 and 15.0 mg/m³; the achieved chamber concentrations were 1.6, 4.58 and 14.83 mg/m³. A particulate aerosol was generated from micronised test substance powder with mean particle size between 4.1 and 4.4 µm (MMAD) and ≥65% of particles with size smaller than 7 µm (MMAD). An additional control group was exposed to air only. All animals were sacrificed on day 8.

There were no clinical sings, bodyweight changes, effects on food and water consumption, macroscopic pathology findings or differences in organ weights that were considered to be attributable to exposure to PTBBA. Samples of a number of organs were preserved, but not prepared for microscopic pathology.

In a 28-day inhalation study with a specific design to evaluate neurotoxicity, the same target concentrations of 4-tert-butylbenzoic acid (99.5%) were exposed to rats by snout-only exposure (HRC, 1995). The mean of achieved chamber concentrations were 1.5, 4.7 and 15.7 mg/m³, 73-80% of particles were <7µm. . Particulate aerosol of p-tert butyl benzoic acid was administered during 6 hours/day on 5 days for 4 weeks to three dose groups of rats. Mean particle diameters (MMAD) were 3.2, 3.9 and 3.9 for low, mid and high dose, and 73-80 % of particles were smaller than 7µm. Another group serving as controls was exposed to air only. Neurobehaviour of all 8 animals/sex/group was examined within the functional observational battery (FOB) prior to the exposure period, at the end of week 1 and 4 of the study. 5 animals/sex/group were subjected to organ weight analysis, macroscopic and microscopic examination of the adrenals, heart, kidneys, liver, lungs, spleen, testes with epididymides, and gross abnormalities. The other 3 animals/sex/group were selected for perfusion fixation and neurohistopathological examination of the brain (at 6 levels), spinal cord dorsal root ganglion, dorsal and ventral root fibres, sciatic nerves (at 2 levels each), Gasserian ganglion, sural and tibial nerves with standard staining procedures (H&E, toluidine blue). The weaknesses of this study were the low dose concentrations chosen, the limited numbers of organs examined by histopathology and the low numbers of animals contributed to the microscopic examination of nervous tissues.

Liver weights of high dose females were significantly higher than control values (+9%). There were no other clinical signs, bodyweight changes, effects on food consumption, macroscopic or microscopic changes in main study rats that were attributable to p-tert butyl benzoic acid. Behavioural observations revealed a slight increase in the incidence of body tremor in the low and high dose group males after 1 week of exposure. After 4 weeks the incidence of body tremor was increased for high dose males. Among high dose males, there was a significant decrease in activity counts with tendency towards decreased rearing counts. Also, facial staining and hair loss occurred with slightly increased frequency in high dose males. The number of males with decreased arousal and urinating/defecating while in the arena was increased in the mid and high dose groups. No similar findings were noted among treated females.

Neither the microscopic examination of the organs examined in the main study nor the examination of the nervous tissues in satellite rats revealed any lesions, which were attributable to 4-tert-butylbenzoic acid.

The occurrence of body tremor might be considered as the most sensitive and earliest neurobehavioural effect. Since no behavioural change was noted for low dose males after 4 weeks of exposure and no body tremor was observed for mid dose males, the NOAEC was considered to be 5 mg/m³ for male rats. The authors proposed a NOAEC of 15 mg/m³ for female rats. Based on the knowledge that the liver was a target organ in other repeated dose studies, the rapporteur's opinion is that due to increased liver weight 5 mg/m³ should also be considered as the NOAEC for female rats.

Neurotoxicity of 4-tert-butylbenzoic acid was obvious from an earlier inhalation study (Shell, 1982). Groups of 8 male and 8 female F344 rats were repeatedly exposed to PTBBA dust at achieved mean concentrations of 0, 12.5, 106 and 525 mg/m³ for 6 h/day on 4 exposure days followed by 3 days (males) or 4 days (females) rest and another 3 day-period with exposure. Scheduled sacrifices were on day 10 for male animals and on day 11 for female animals. Mean particle diameters were 4.1, 3.6 and 4.3 µm (MMAD) for the control, low, mid and high dose groups.

Unscheduled deaths occurred at concentrations of 106 and 525 mg/m³. In the mid dose group, two males died on days 2 and 8 and one female died on day 8. Seven males of the high dose were found dead on days 1 until day 6 (and thereby limiting the statistical comparison of some test parameters); mortalities of three high dose females were seen on day 3 and 11.

Urine staining of the urogenital region and abnormal neurobehaviour were seen in exposed animals consisting of fore and hind limb paralysis, hunched posture, tremors, convulsions, gait abnormalities, prolapsed penis, hypoactivity, and abnormal respiration with symptoms beginning on day 3 of the study in the mid dose groups and on day 1 of the high dose groups. High dose females had significant decreased in haemoglobin concentration and hematocrit; a dose-related increase in mean white blood cell counts was found in mid and high dose groups of both sexes. Clinical chemistry examinations revealed reduced activity of alkaline phosphatase in all female dose groups and mid and high male dose groups, reduced albumin and total protein levels in mid and high dose females, reduced cholesterol concentrations in all female dose groups, increased activity of ASAT in high dose females and the surviving male of the high dose group. ALAT activities were increased in the mid and high dose females and in the surviving high dose male.

Macroscopic findings were primarily noted in animals exposed to the mid and high concentrations. They consisted of perineal and abdominal urine staining, dehydration, white powder on the haircoat, small red thymus, bright red lungs, pinpoint red gastric foci, small soft testes, focal epididymal lesions, enlarged tan livers, reduced digesta and body fat stores.

Males and females of the mid and high dose groups showed dose-dependently significant loss of body weight during the study period. Absolute and relative organ weights of the liver and kidneys were increased in animals of these dose groups; a similar tendency was also evident for the lung to body ratio. Absolute and relative weights of the testis were reduced for males of the mid and high dose groups. A dose-related reduction in mean number of sperm per testis (left testis of all surviving rats) was recorded for all dose groups compared to the controls.

Microscopically, treatment-related lesions were seen in the kidneys of rats from all dose groups, the livers, spinal cord, testis, epididymides, and thymus of rats from mid and high dose groups.

Kidney lesions were characterised by bilateral multifocal cytoplasmic eosinophilia (pallor) of cortical tubular cells and in rats of the mid and high dose groups vacuolation was found. Vacuolar degeneration (negative for lipid staining) was also found in peripherilobular/periportal or panlobular hepatocytes and, in rats of the high dose groups, the rate of mitotic cells was increased in areas of less affected hepatocytes. Severe focal or regional poliomyelomalacia has been observed in the spinal cord of rats exposed to the mid and high concentrations. Lesions of the central nervous system were reported for animals, which demonstrated clinical signs of paraplegia indicating that thoracal and more distal segments were affected. Neuropathological lesions such as neuronal degeneration and loss, vacuolation, microgliosis and congestion were localised in the central area of the grey matter lesions and in the ventral funiculi region of white matter. Multifocal to diffuse degeneration of the germinal epithelium has been found in the testes (Lu et al., 1987). Males of the mid dose group developed severe tubular changes consisting of absence of late spermatids, reduction in spermatogenic cell types, giant cell bodies and cellular debris, and atrophy and inflammation of epididymides. Lesions were more extensive than those seen in males of the high dose and were thought to be reflecting the earlier time of death in unscheduled mortalities at the high dose group.

Lymphocytic necrosis and atrophy in the cortical region of the thymus, plus medullary congestion and haemorrhage were observed in three males exposed to the high concentration and in single male and female rats of the mid dose groups. Most of rats with thymic lesions belonged to those dying during the study.

Compared to the study design of actual testing guidelines for repeated inhalation studies (e.g., OECD 412, Annex V B.8 method) the main weaknesses of this study were its short exposure duration, the lack of data from neurofunctional testing battery, lack of water and feed consumption data and urinalysis, the restricted panel of organs processed for histopathology (spinal cord, nasal passages, trachea, larynx, lungs, liver, kidneys, right testis and all macroscopic lesions, unknown number of levels examined of the spinal cord and nasal tissues). Nevertheless the data presented were deemed to give valid information on the toxicity of the test substance, identified targets were consistent with data from other studies.

No NOAEC could be delivered from this 11 day-inhalation study, the LOAEC was 12.5 mg/m³ (6 h/d, 7 exposure days).

Dermal

The subchronic dermal toxicity of aqueous solutions (1 ml/kg/bw) containing the diethanolamin (DEA) salt of 4-tert-butylbenzoic acid at a ratio of 1.7:1.0 was determined in F344 rats (Cagen et al., 1989, Lu et al., 1989). Groups of 20 male and 20 female rats were exposed topically on 5 days/week with dosing solutions that resulted in daily exposures of 0, 17.5, 35, 70, or 140 mg/kg 4-tert-butylbenzoic acid. For these dose groups, the mean daily exposure to DEA was 0, 11.7, 21.6, 41.3, or 82.6 mg/kg. After 7 weeks of treatment, seven male and seven female rats from each group necropsied. The treatment continued on the remainder of the rats until necropsy after 13 weeks of exposure. Study examinations included daily observation for clinical signs of toxicity, feed and water consumption, body weight, macroscopic findings, organ weights of lungs with trachea, larynx, liver, kidneys, brain, heart, testes or uterus, and spleen, and histopathology on ≥26 organs/tissues (including those weighed and sciatic nerve and spinal cord). At 7 and 13 weeks of exposure, samples of urine and blood were obtained and examined for standard parameters of hematology, clinical chemistry and urinalysis. In addition to histopathology on the right testis, testes weight and, on the left testis, sperm counts were determined and LDH-x enzyme assay as a measure for surviving spermatocytes and spermatids was performed in male rats following 7 and 13 weeks of treatment.

Treatment did not produce overt clinical signs of toxicity and did not cause irritation to dermal exposure sites. Exposure to the two top doses resulted in decreased weight gain, mean feed consumption was not different from that of the control groups. Microcytic hypochromic anemia was present in animals of the two top doses; erythrocytic microcytosis at normal erythrocyte counts occurred at two low concentrations. A significant increase in urine volume occurred during week 13 in the two top dose male groups and the top female group. After 7 and 13 weeks, cholesterol concentrations were reduced in all dose groups, and the levels of BUN and phosphorus were increased for male and female rats of the two top doses. Dose-related significant increases in relative and absolute hepatic and renal weights were seen at all concentrations. Exposure to males to the two highest concentrations caused significantly decreased relative testis weight, sperm counts and LDH-X enzyme activity.

Exposure-related pathologic changes confined to three organ systems of rats of the two highest concentrations were cytoplasmic vacuolation in the liver, pallor, dilatation, degeneration and regeneration of distal convoluted tubular epithelium, tubular casts,

interstitial nephritis and papillary necrosis of the kidneys; and moderate to severe diffuse tubular degeneration with absence of late spermatids, reduced number of spermatogenic cell types, and giant cell formation in the testes. Liver cell vacuolation was also evident in female rats treated with 17.5 and 35 mg/kg p-tert butyl benzoic acid. This lesion was characterised as multifocal to diffuse perilobular to panlobular, lipid-positive vacuolation of hepatocytes. Accompanying aberrations in clinical chemistry values suggested altered hepatic and renal function. In males exposed daily to ≥70 mg/kg PTBBA, the testicular effects were marked; no effects were detected in rats exposed to 17.5 or 35 mg/kg of 4-tert-butylbenzoic acid.

Although rats of this study were dermal exposed to preparations of 4-tert-butylbenzoic acid and DEA, a contribution of DEA, especially on the liver metabolism can not be ruled out. In view of the observation, that effects in the same target organs were similar to those mentioned after repeated oral or inhalation exposures they were attributed to 4-tert-butylbenzoic acid.

From this dermal study the LOAEL was 17.5 mg/kg bw/day.

In a second dermal study (Shell, 1975), groups of 8 male and 8 female rats (Carworth Farm E strain) received 0. 7.5, 15, 30 and 60 mg/kg bw/d 4-tert-butylbenzoic acid (0.2 mg/kg of 3.75, 7.5, 15 or 30% w/v solutions of 4-tert-butylbenzoic acid in DMSO) topically on shaved skin for 28 days. Body weights were recorded daily. Four animals/sex/group were necropsied at the end of the study and the liver, kidneys, and the gonads were examined histologically.

Growth rates were reduced in males and during the first two weeks in female rats exposed to 30 and 60 mg/kg bw/d resulting in significantly lower final body weight of males of these dose groups.

Dose-related significant increases in absolute and relative liver weights were seen in female rats of all dose groups (+11, 23, 27, 30%) and in male rats exposed to 15 mg/kg/d and above (+8, 11, 17%). Increased relative weights of kidneys were observed in two top doses of female rats, and decrease in relative and absolute testes weights were determined for male rats receiving 60 mg/kg/d.

Histopathology of the testes revealed a degeneration of germinal epithelium in males exposed to 60 mg/kg/d. No other toxic effect was observed in the liver and the kidneys of the four animals/sex/group examined except an increased basophilia of centrilobular hepatocytes that was considered of uncertain significance.

The LOAEL was 7.5 mg/kg bw/d this study was flawed by the small numbers of test parameters and animals and a poor documentation (summary, 2 tables and 1 figure available).

Oral

In an oral 90 day study, albino Carworth Farm rats (10 animals/sex/group) were orally administered to diet containing doses of 0, 100, 316, 1000, 3160 and 10000 ppm of 4-tert-butylbenzoic acid (calculated from food intake 0, 6, 21, and 75 mg/kg bw/d for males, 0, 8, 27, 89 mg/kg bw/d for females, for doses up to 1000 ppm, no calculation on the top two doses) for 90 days (Hunter et al., 1965). Feed consumption and body weight were monitored and urinalysis, hematology and clinical chemistry (limited test parameters), gross and microscopic examinations were performed.

Unscheduled deaths of 9 of ten high dose males occurred by day 34, all females receiving 10000 ppm died by day 53. From the group receiving 3160 ppm, two males died by day 42

and six further males were killed moribund. Two mortalities and one female rat to be killed were also seen in the female group at 3160 ppm. Hematuria has been observed in one male and two females receiving 3160 ppm. Hind limb paralysis was reported for one male and one female exposed to diet concentration of 3160 ppm and one female at 1000 ppm. Kyphosis was observed in three rats receiving 3160 ppm and suspected to occur secondarily to chronic renal failure.

Final body weights were significantly depressed in males at diet concentrations of 316 and above and in female rats at 1000 ppm and above. The feed consumption was reduced in the two top doses to 50-70% of the control values and was not affected in the other dose groups. No treatment-related effect was seen on hematology parameters other than reduced erythrocyte counts in the surviving male treated with 10000 ppm and a shift towards increased percentages of neutrophils and reduction in lymphocyte counts at diet concentrations of 3160 ppm (surviving males and females) and of 10000 ppm (1 male survivor). Clinical chemistry findings showed reduced levels of total protein for male groups receiving 100 to 1000 ppm; urea concentrations were increased in males and female rats at diet concentrations ≥1000 ppm in a dose-related fashion.

Urinalysis revealed increased urine volume and reduced urine osmolality in rats treated with diet concentrations at 3160 ppm and above; protein concentrations were elevated in animals the 10000 ppm dose groups.

Relative organ weights of the liver and the kidneys increased at all diet concentrations. The testes to body ratio decreased in all male dose groups.

Gross findings in dying and sacrificed rats of the two top doses showed congested and speckled livers and hydronephrosis, hydroureter, ureteral obstructions, hematuria in the urinary tract. Bilateral atrophy of the testes was found in males of all dose groups. Microscopically, sinusoidal congestion and fatty degeneration of centrilobular hepatocytes were found (the 'fatty' nature was not confirmed by specific staining procedures). Hydronephrosis was confirmed by histopathological examination for males at ≥3160 ppm and female rats at 10000 ppm. Intra-luminal cell debris, necrosis of the tubular epithelium, and papillary necrosis were reported as the causes of the obstructive urinary tract lesions.

Renal tubular necrosis and papillary necrosis was evident in treated male and female rats of all dose groups. The testes atrophy was related to degenerated epithelium of seminiferous tubules.

A NOAEL could not be determined in this early study; 100 ppm (6 mg/kg bw/d for male rat, 8 mg/kg bw/d for female rats) is the LOAEL for oral subchronic administration of 4-tert-butylbenzoic acid.

Table 4.2 Repeat-dose toxicity of 4-tert-butylbenzoic acid in rats

Study design (Reference)	Delayed mortalities	Growth retardation	Neurotoxicity	Liver toxicity	Urinary tract toxicity	Toxicity in reproductive organs	Haemo-toxicity	Immuno-toxicity	NOAEL (C)
Inhalation									
28d-study, rat, 0, 1.5, 5, 15 mg/m³ (HRC, 1995)	-	-	15 mg/m³ : Tremor, hypoactivity	15 mg/m³ : Liver weight↑	-	-	-	-	NOAEC 5 mg/m³
11d-study, rat, 0, 12.5, 106.1, 525.2 mg/m³ (Shell, 1982)	≥106mg/m³:	≥106 mg/m³: Emaciation	≥106 mg/m³: Tremor, paralysis, convulsions, ataxia, prolapsed penis, hypoactivity. Severe focal/ regional poliomyelo-malacia + gliosis of spinal cord	≥12.5 mg/m³: Serum cholesterol↓, alkaline phosphatase↓, ≥106 mg/m³: serum ALAT↑,prot↓ liver weight↑, vacuolar degeneration of hepatocytes 525 mg/m³: serum ASAT↑	≥12.5 mg/m³: Pallor of cortical tubules ≥106 mg/m³: kidney weight↑ vacuolar degeneration of cortical tubules	≥12.5 mg/m³: Hypospermia ≥106 mg/m³: Testes: atrophy weight↓, degeneration of germinal epithelium. Epididymides: atrophy	525 mg/m³: Hb↓, Htc↓, WBC↑	≥106 mg/m³: Thymus: cortical atrophy	LOAEC 12.5 mg/³
Oral									
90d-study, rat 0, 100, 316, 1000, 3160, 10000 ppm (Hunter et al., 1965)	≥3160 ppm	≥316 ppm Final body weight↓ ≥3160 ppm Feed consum↓	1000 ppm on Day 90 and at 3160 ppm after Day 70: hind leg paralysis, no data on nervous tissue morphology	≥100 ppm Serum prot↓, liver weight↑ ≥3160 ppm: speckled liver, degeneration of hepatocytes	≥100 ppm: Kidney: weight↑, tubular cell + papillary necrosis ≥1000 ppm: serum urea↑ ≥3160 ppm:	≥100 ppm: Testes weight↓, atrophy, degenerated tubuli	10000 ppm: RBC↓, neutrophiles%↑	Nd	LOAEL 100 ppm (≈ 6 mg/kg bw/d in male rats, 8 mg/kg bw/d in female rat)

					diuresis↑, hematuria, hydro-nephrosis, hydroureter, tubular damage				
Dermal									
7/13 wk-study, rat, 0, 17.5, 35, 70, 140 mg/kg bw/d (Cagen et al., 1989)	-	≥70 mg/kg: Body weight gain↓	-	≥17.5 mg/kg: Serum cholesterol↓, liver weight↑, vacuolar degeneration of hepatocytes	≥17.5 mg/kg: Kidneyweight↑ ≥70 mg/kg: Urine:volume↑ serum BUN↑, phosphorus↑ Kidney: degeneration + regeneration of distal convoluted tubules, interstitial inflammation, papillary necrosis	≥70 mg/kg: Testis weight↓ hypospermia, degeneration of germinal epithelium	≥17.5 mg/kg: Microcytosis of RBC ≥70 mg/kg: hypochromic anemia	-	LOAEL 17.5 mg/kg bw/d
28 d-study, rat 0, 7.5, 15, 30, 60 mg/kg/d, (Shell, 1975)	-	≥30 mg/kg Body weight gain↓	Nd	≥7.5 mg/kg: Liver weight↑	≥30 mg/kg Kidney: weight↑,	60 mg/kg Testes weight↓, degenerated tubuli	Nd	Nd	LOAEL 7.5 mg/kg bw/d

- no adverse effect observed Nd: no data available

4.1.2.6.2 Studies in humans

No studies are available.

4.1.2.6.3 Summary of repeated dose toxicity

No information is available on the effects of repeated exposure in humans.

- Systemic toxic effects in animals after repeated inhalation, oral or dermal exposure: In animals there are data for all routes of exposure. Although all animal studies conducted have weaknesses in the test design and/or documentation and none of them was in full concordance with actual requirements for repeat-dose toxicity testing, consistency of findings with respect to the target organs and nature of the effects of systemic toxicity were considered to give sufficient confidence to enable assessment of repeat-dose toxicity.

  The target organs for repeat dose toxicity of 4-tert-butylbenzoic acid were the central nervous system, liver, kidneys, testes, epididymides, hemopoietic system and the thymus (effects are summarised in Table 4.3).

  Similar lesions in the liver, kidney, male reproductive organs and peripheral blood were identified across all studies regardless of the route of exposure. Neurotoxicity was produced after repeated inhalation and oral administration. No clinical signs of abnormal neurobehaviour or morphological abnormalities of nervous tissues were reported from the dermal study.

  Since no mechanistic data could plausible demonstrate a test species specific effect, all toxic effects observed in rats after repeated 4-tert-butylbenzoic acid were considered to be of toxicological significance to human health.

  Based on the most sensitive adverse effect observed in the studies available (see Table 4.3), the no (or lowest) observed adverse effect levels for systemic toxicity of 4-tert-butylbenzoic acid were determined.

  Inhalation

  a $NOAEC_{sys}$ of 5 mg/m³ (from 28 day study, HRC, 1995),

  the $LOAEC_{sys}$ of 12.5 mg/m³ (corresponding to 1.5 mg/m³ in a 90 day study

  (from 11 day study, Shell Development Company, 1982)

  Using Haber's rule to extrapolate to a 90 day study design, 12.5 mg/m³ of PTBBA corresponds to 1.5 mg/ m³ which is 166-fold below the limit concentration for harmful/R48/20.

  The only indications on local effects on the respiratory tract were seen in the 11 day-inhalation study (Shell, 1982), where rats exposed to 106 mg/m³ and above showed bright red lungs and a tendency for increase in relative lung weight. Microscopic examination of tissues from the nasal passages, the larynx, trachea and lungs of the

respiratory tract were conducted and did not indicate a PTBBA related effect. Samples of the lungs but no other respiratory tract tissues were examined histopathologically in all rats of the 28 day-inhalation study (HRC, 1995). No treatment related effect was observed in the lungs of rats exposed to PTBBA.

It is concluded that based on the limited data available repeated inhalation of PTBBA did not cause respiratory tract toxicity.

The $NOAEC_{local}$ for toxic effects on the respiratory tract was 525 mg/m³

(from 11 day study, Shell, 1982).

Oral

a LOAEL of 100 ppm (6 mg/kg bw/d)

(from 90 day study, Hunter et al., 1965),

6 mg/kg PTBBA producing kidney and testis toxicity is markedly lower than the critical concentration of 50 mg/kg bw/d for harmful/R48/22.

Dermal

a LOAEL sys of 7.5 mg/kg/d

(from 28 day study, Shell, 1975).

7.5 mg/kd bw/d corresponds to 2.3 mg/kg bw/d in a 90 day study, which is markedly lower than the critical dose of 100 mg/kg bw/d for harmful/R48/21. This is supported by the LOAEC of the 7/13 week study of Cagen et al., 1989, where LOAEC was 17.5 mg/kg bw/d (the lowest dose tested) was significantly below the limit concentration of 100 mg/kg bw/d.

Based on the above data, 4-tert-butylbenzoic acid should be classified "T, R48/23/24/25, Toxic by inhalation, in contact with skin and if swallowed". The adverse effect levels were far below the guidance values for the classification as harmful. Therefore the currently applied classification should be replaced. In September 2007 the TC C&L agreed T; R48/23/24/25.

- Discussion on target organ toxicity:

  Growth retardation

  The observation that feed consumption was not changed by treatment (Cagen et al., 1989) or reduction in feed consumption was seen only in high doses of 4-tert-butylbenzoic acid (Hunter et al., 1965) support the conclusion that reduced gain of body weight and reduction of final body weight can be interpreted indicative for non-specific toxic effect of PTBBA.

Neurotoxicity

Regional poliomyelomalacia and responsive gliosis of the spinal cord described in the Shell study (1982) can be associated to the fore and hind limb paralysis and gait abnormalities that was observed in the 11 day-inhalation study at particle concentrations of 106 mg/m³ and above. Similar lesions might be expected for animals with hind limb paralysis receiving diet concentrations of 1000 ppm and above of the 90 day study (Hunter et al., 1965). The fact that nervous tissue damage has not been observed in the dermal study is no proof for the absence of neurological effects since methods applied in all repeat-dose studies are routine staining procedures which may be insufficient to detect specific lesions in cellular compartments of the nervous system.

Urinary tract toxicity

4-tert-Butylbenzoic acid affected the urinary system by all exposure routes. The tubular epithelium of the distal cortical convoluted tubules and papillary region (renal pelvis) seemed to be the primary sites of 4-tert-butylbenzoic acid toxicity. Increased diuresis, hematuria, tubular casts, regenerative epithelium, interstitial inflammation, hyrdronephrosis and hydroureter were associated lesions that can be considered as the death-related cause in the oral study of Hunter et al. (1965).

Liver toxicity

Increased activity of serum transaminases (Shell, 1982), speckled, enlarged appearance of the liver were consistent with the liver cell toxicity observed in all repeat-dose studies available. The increase in liver weights were considered as indicative for hepatotoxicity in those studies (HRC, 1995, Shell, 1975), where overt morphological lesions or biochemical findings could not be observed or were unknown due to the lack of examination since hepatocyte cytotoxicity in other studies were associated to increased liver weights in the other studies**.** Reduced serum cholesterol levels and fatty vacuolation of liver cells can be assumed to reflect a disturbance of lipid metabolism. This assumption was supported by in vitro data on isolated hepatocytes showing that PTBBA inhibited fatty acid synthesis and increased medium and long chain acyl CoA esters (McCune et al., 1982).

Toxicity in reproductive organs

Testicular lesions attributable to 4-tert-butylbenzoic acid occurred in rats exposed via all exposure routes. Similar effects were observed in the studies available, which were characterised by the degeneration of germinal epithelium resulting in disturbance of spermatogenesis at several stages of spermatogenic cells. The presence of multinucleated giant cells in the luminal of seminiferous tubules of testes was indicative for a more chronic process. Corresponding secondary changes were atrophy and inflammatory responses of the epididymides.

Toxic effects on the hemopoietic system

Signs of microcytic hypochromic anemia were found at diet concentration of 10000 ppm (Hunter et al., 1965), at particle concentration of 525 mg/m³ (Shell, 1982) and at 70 mg/kg bw/d of 4-tert-butylbenzoic acid applied topically (Cagen et al., 1989). Indications for increased erythrocyte destruction were not identified, other causes might be more likely, however unknown.

Increased WBC counts and increased percentages of neutrophilic granulocytes observed at 525 mg/m³ of the inhalation study of Shell (1982) and at 10000 ppm of the oral study of Hunter and his colleagues (1965) were presumably related to inflammatory responses to the damage in target organs.

Immunotoxicity

Due to the scarce database the toxicological significance of cortical atrophy of the thymus following lymphocytolysis remains uncertain (Shell, 1982). Most of the rats affected were those dying spontaneously.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies in vitro

Bacterial systems

A bacterial mutation test was negative (Hoechst AG, 1978). Five doses ranging from 4 to 2500 µg/plate were tested with and without Aroclor-induced S-9 mix in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537. The highest dose induced strain-specific toxic effects (decrease in revertant frequencies). Even though no confirmation experiment was performed it can be concluded with sufficient reliability, that PTBBA does very likely not induce gene mutations.

In vitro systems with mammalian cells

An *in vitro* micronucleus test with 4-tert-Butylbenzoic acid was positive with metabolic activation in Chinese Hamster V79 cells (RCC-CCR, 2007). Cells were treated with doses of 375.0, 750.0, and 1500.0 µg/ml in dimethylsulfoxide. Cell cultures were exposed for 4 h in the presence and absence of metabolic activation (Aroclor-induced rat liver S-9 mix) and sampled 20 h after treatment. The highest applied dose led to visible precipitation with metabolic activation; no clear toxicity was observed with and without S-9 mix.
Treatment with S-9 mix induced weak increases in micronuclues rates at 750 mg/ml (3.2 %) and 1500 µg/ml (4.95 %; 1.6 % in control). Treatment without S-9 mix was negative although a sporadic increase of the micronucleus rate at 375.0 µg/ml (2.15 %) but not at higher doses was observed. Due to the positive result with metabolic activation no confirmation experiment was performed.
The *in vitro* micronuclues test was performed in compliance with the draft proposal for the OECD Guideline for the Testing of Chemicals "*In vitro* micronucleus test" (No. 487).

4.1.2.7.2 Studies in vivo

In vivo systems with mammals

An in vivo chromosomal aberration test with rats according to OECD TG 475 was negative for single oral gavage doses of 600 (males) or 300 (females) mg/kg bodyweight (RCC-CCR, 2000). Five animals were used per group, bone marrow cells were sampled 24 h and 48 h after

treatment. Treatment led to toxic reactions in both genders and lethal effects in males (2/6). Pretests on toxicity demonstrated that in males lethal effects were observed for doses of 900 mg/kg (1/2) and 1000 mg/kg (1/2); in females lethal effects were observed for doses of 500 mg/kg (1/2), 600 mg/kg (1/2) and 800 mg/kg (2/2). A weak reduction of mitotic indices was observed at 24 h sampling in females (6.76 % in treated males, 5.02 % treated females vs. 7.24 % in control group).

4.1.2.7.3 Summary of mutagenicity

4-tert-Butylbenzoic acid did not induce gene mutations in several Salmonella typhimurium strains. An *in vitro* micronucleus test with 4-tert-Butylbenzoic acid was weakly positive with metabolic activation in Chinese Hamster V79 cells.

An in vivo test on chromosomal aberrations in rats was negative for doses which correspond to the MTD. Oral bioavailability can be assumed from the physico-chemical data. This is in line with the fact that toxic effects were observed after acute and subacute oral application of low doses of the substance as well as the weak local effects (reduction of mitotic indices) in the *in vivo* chromosomal aberration test. There is sufficient evidence to conclude, that a clastogenic potential of ptBBA observed *in vitro* is unlikely to be expressed in germ cells *in vivo*.

However, due to the positive *in vitro* micronucleus test and the fact that clastogenicity and aneugenicity were not distinguished in this test there is concern for local clastogenic effects and aneugenic effects cannot be excluded. Therefore further testing for clarification is recommended, preferably a combination of an *in vivo* COMET assay (directly exposed tissue and liver) and a bone marrow micronucleus test.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

In vivo studies

No data available.

4.1.2.8.2 Studies in humans

No data available.

4.1.2.8.3 Summary of carcinogenicity

At present, the carcinogenic potential of 4-tert-butylbenzoic acid has not been examined in human populations and no animal studies have been conducted. No conclusion can be drawn on the carcinogenic potential of the substance. However, positive data from in vitro

micronucleus testing may give concern on genotoxic properties of 4-tert-butylbenzoic acid. If further testing will be required, their results have to be taken into considerations.

The sodium salt of benzoic acid did not produce increases in tumor incidences in carcinogenicity studies on mice (Toth, 1984) and rats (Sodemoto & Enomoto, 1980; study with restricted validity because of high mortality rates due to infectious pneumonia).

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Studies in animals

During a study with Wistar rats (Hoechst, 1987) focussing on *male* fertility, ten males per group were fed diets containing 0, 20, 100, or 500 ppm PTBBA continuously for a period of 70 days before starting with mating trials. From the food consumption data it was calculated that dietary levels accorded to a mean daily intake of 1.6 (20 ppm), 7.9 (100 ppm) and 41 (500 ppm) mg PTBBA/kg body weight. During the exposure period the animals were checked regularly for general condition, behaviour, body weight and food consumption. Each male was then mated to two non-exposed virgin females for a period of one week (first mating trial) and the females checked daily for cyclicity and sperm. Proof of fertility was taken from successful impregnation of at least one of the two females. Males that had not been fertile during the first trial were kept for another 70 days without dietary exposure to PTBBA and then were again mated to virgin females for a period of one week (second mating trial). The latter were designated as recovery group. The following endpoints were recorded: length of gestation, numbers of live and dead borns, sex, weight and any externally visible anomalies of the new-borns, which were finally sacrificed. Males were terminated at delivery of their impregnated dams or at the end of the mating trials and macroscopically investigated. Organ weights were taken of brain, heart, liver, spleen, kidney, testes and epididymides. Testes, epididymides, prostate and seminal vesicles were subjected to histopathological investigation. Females were terminated either one day after delivery or 25 days after the last mating trial and macroscopically investigated and numbers of implantation sites counted.

Lower dietary levels of 20 and 100 ppm PTBBA did not result in any weight gain impairment of the animals. At the 500 ppm level reversible reduction in body weight was observed in treated animals. Males gained less body weight during the exposure period resulting in body weights 14 % lower in comparison to the controls after 70 days of exposure, yet continued to develop normally after the animals had changed to their usual diet.

Ten males of the 20 ppm exposed group and 9 males of the 100 ppm exposed group revealed to be fertile during the first mating trial (Table 4.4). Eight males of the 20 ppm group, 7 males of the 100 ppm group and 9 males of the control group impregnated both of the two females. One male of the 100 ppm group was not successful in impregnating but sired one of its females. No pregnancies were produced during the first mating interval from males exposed to dietary levels of 500 ppm. Three males inseminated one female each; however, no pregnancies resulted, whereas from the other 7 males no sperm was detected in vaginal smears of their female partners.

Table 4.3 Outcome of the 1st mating trial (Hoechst, 1987)

1. Mating trial	Controls	Treatment groups		
		20 ppm	100 ppm	500 ppm
Males investigated (n)	10	10	10	10
Fertile males [successful in impregnation] (n)	10	10	9	0
Female partners investigated (n)	20	20	20	20
Females sperm positive /pregnant	19	18	16	0
Females sperm positive /nonpregnant	0	0	2	3
Females neither sperm positive nor pregnant	1	2	2	17

Table 4.4 Outcome of the 2nd mating trial (Hoechst, 1987)

2. Mating trial			Recovery groups	
			100 ppm	500 ppm
Males investigated (n)			1	10
Fertile males [successful in impregnation] (n)			1	10
Female partners investigated (n)			2	20
Females sperm positive /pregnant			1	18
Females sperm positive /nonpregnant			1	1
Females neither sperm positive nor pregnant			0	1

During the second mating trial 70 days after the end of the treatment period the recovery group males revealed all to be fertile (Table 4.5). Eight males of the former 500 ppm group impregnated both of their female partners, while two males of this group and one male of the former 100 ppm group impregnated only one female partner each.

No treatment-related effects were observed for duration of the gestational period and on parturition. There were no differences in the numbers of live borns per litter, in sex ratio and in mean body weights of the new-borns between the controls and the treatment groups. No externally visible anomalies in new-borns were recorded.

In the parental males organ weights for brain, heart, liver, spleen and kidneys of the treated groups did not differ from those of the controls. Also testes weights in the 20 and 100 ppm group did not differ from those of the controls. In males of the 500 ppm group however, after recovery for more than 70 days, mean testes weights were reduced (2.76 g) in comparison to that of the controls (3.14 g).

Histopathological evaluation of the male reproductive organs did not reveal any differences in comparison to the controls for animals exposed to the 20 and 100 ppm level. For animals exposed to the 500 ppm level minor lesions at the germinative epithelium were found which were confined to few tubules only. No histopathological changes were found for the 500 ppm group for prostate, seminal vesicles and epididymides and its sperm.

A NOAEL/$_{\text{male fertility}}$ of 20 ppm (according to 1.6 mg PTBBA/kg bw/d) can be derived from the study based on the finding of infertility/inability to impregnate at dietary dosages of 100 ppm (according to 7.9 mg PTBBA/kg bw/d).

No data on possible female fertility impairment or other functional studies could be identified in the available database.

Additional information on reproductive organ toxicity of PTBBA is available in the database from studies on sub-/chronic toxicity testing of the compound (c.f. 4.1.2.6).

In a subchronic oral toxicity study (Hunter et al., 1965) laboratory bred albino Carworth Farm rats in groups of 10 animals/sex were fed diets containing 0, 100, 316, 1000, 3160, or 10 000 ppm PTBBA (calculated from food intake as 0, 6, 21, and 75 mg/kg bw/d for males, 0, 8, 27, 89 mg/kg bw/d for females with no calculation on the top two doses) for a period of 90 days. Dietary levels of 3160 and 10 000 ppm resulted in high percentages of premature deaths or animals to be killed in extremis, whereas no deaths were observed in the three lower exposure groups. At the end of the study terminal body weights were statistically significantly lower ($p<0.01$) than those of the controls for the 1000 and 316 ppm exposure groups. Besides absolute and relative organ weight impairment of the liver and the kidney also mean absolute and relative testes weights were statistically significantly ($p<0.05$) reduced in the 1000 (to 1.21 g) and 316 ppm (to 2.67 g) exposure groups in comparison to the controls (3.45 g). Besides renal tubular and papillary necrosis in the 1000, 316 and 100 ppm exposure groups, the histopathological investigations also revealed testes atrophy caused by destruction of the epithelium of the seminiferous tubules (no data provided). The authors indicate that atrophy of the testis was found even in the lowest dosage group of 100 ppm. Thus, an NOAEL on male reproductive organ toxicity could not be determined.

A LOAEL/$_{\text{testes toxicity}}$ of 100 ppm (according to 6 mg PTBBA/kg bw/d) can be derived from the study based on the findings of testes weight reduction and effects on the germinative epithelium.

In a subchronic dermal toxicity study (Lu et al., 1987, Cagen et al., 1989) Fischer 344 rats in groups of 20 animals/sex were treated topically (once a day /five days a week) on skin clipped free of hair with 1.0 ml/kg of an appropriate formulation of PTBBA and diethanolamine salt prepared in deionized water (simulating cutting fluid) for either 7 weeks (7/sex/group) or 13 weeks (13/sex/group). Treatment was calculated to result in daily exposures of 0 (deionized

water), 17.5 (*11.7)*, 35 (*21.6*,) 70 (*41.3)* and 140 (*82.6*) mg PTBBA (*resp. mg diethanolamine*) per kg body weight. During this study besides absolute and relative testis weight determinations also sperm head count and LDH-X enzyme assays (from the right testis) were performed. Dermal exposures as high as 140 mg PTBBA/kg bw/day did not result in exposure related deaths or any clinical signs of toxicity. Significantly lower body weights and body weight gain were observed for males and females exposed to 140 mg/kg/day and for females exposed to 70 mg/kg/day. Besides absolute and relative organ weight impairment of the liver and the kidney at dermal exposures of already 17.5 mg/kg/day at both 7 and 13 week treatment periods, also reductions of absolute and relative testes weights were observed, which were statistically significantly different from the controls at daily dermal exposures of 70 and 140 mg/kg/day at 7 and at 13 weeks (Table 4.6). Also sperm head count and LDH-X enzyme activities were reduced in these two groups as compared to those of the controls following 7-week or 13-week dermal application. Exposure-related microscopic lesions were principally confined to the liver, kidneys and testes. Testicular changes attributable to PTBBA primarily occurred in rats of the 70 and 140 mg/kg bw/day exposure groups. It is reported that lesions were characterised by moderate to severe diffuse seminiferous tubular degeneration. Most affected tubules were reported to contain spermatogonia, primary and secondary spermatocytes, early spermatids, and Sertoli´s cells but were devoid of late spermatids. Occasionally, few seminiferous tubules in the same testis contained only Sertoli cells and a few spermatogonia. Testicular giant cells were reported to be quite numerous in the degenerative tubules of the rats of these two exposure groups and occurred in even greater numbers within epididymal tubular lumina. A reduction in number of spermatogenic cell types and the absence of late spermatids were the most striking findings in the rats after 7 or 13 weeks exposure to PTBBA.

In a further dermal study, c.f. 4.1.2.6, (Shell, 1975), groups of 8 male (Carworth Farm E strain) received 0. 7.5, 15, 30 and 60 mg/kg bw/d 4-tert-butylbenzoic acid (0.2 mg/kg of 3.75, 7.5, 15 or 30% w/v solutions of 4-tert-butylbenzoic acid in DMSO) topically on shaved skin for 28 days. Body weights were recorded daily. Four animals/group were necropsied at the end of the study and the liver, kidneys, and the gonads were examined histologically.

Growth rates were reduced in males exposed to 30 and 60 mg/kg bw/d resulting in significantly lower final body weight of males of these dose groups.

A decrease in relative and absolute testes weights was determined for male rats receiving 60 mg/kg/d. Histopathology of the testes revealed a degeneration of germinal epithelium in males exposed to 60 mg/kg/d.

A $NOAEL/_{testes\ toxicity}$ of 30 mg/kg bw/d can be derived from this study based on the findings of testes weight reduction and effects on the germinative epithelium at 60 mg/kg bw/d

Table 4.5 Influence of dermal application of PTBBA to rats on testes parameters

(Studies by Lu et al. (1987) and Cagen et al. (1989)

	PTBBA in males (mg/kg bw/d)				
	0.0	17.5	35	70	140
Week 7, n=7					
Mean body weight (g)	289.4	289.6	296.3	277.6	261.0*)
Mean abs. left testis weight (g)	1.45	1.40	1.49	0.85*)	0.48*)
Mean abs. right testis weight (g)	1.40	1.52	1.47	0.8*)	.059*)
Mean rel. Testis weight (g)	0.99	1.10	1.00	0.61*)	0.41*)
Mean sperm count (Mio)/testis	181	163	204	14	0.1
Week 13, n=13					
Mean body weight (g)	334.1	324.2	319.7	311.4*)	277.7*)
Mean abs left testis weight (g)	1.54	1.52	1.55	0.85*)	0.62*)
Mean abs right testis weight (g)	1.52	1.51	1.54	0.84*)	0.65*)
Mean rel. Testis weight (g)	0.92	0.94	0.97	0.54*)	0.46*)
Mean sperm count (Mio)/testis	174.4	166.3	175.3	7.8	0.08

*) ($p<0.01$)

A $NOAEL_{testes\ toxicity}$ of 35 mg PTBBA/kg bw/d can be derived from the study based on the findings of testes weight reduction, hypospermia and degeneration of the germinative epithelium at the higher exposures.

In a short term inhalation toxicity study, c.f. 4.1.2.6, (Shell, 1982; Lu et al., 1987) groups of Fischer 344 rats were exposed to either (i) concentrations of 495, 668, 958, or 1802 mg of PTBBA dust in air/m^3 for 4 hours (6 animals/group) or (ii) to concentrations of 12.5, 106, or 525 mg of PTBBA in air/m^3 6 hours/day for 4 consecutive days, followed by 3 days rest and 3 more days of exposure (8 animals/group). Control groups may have been inappropriate, as these were not dust exposed but exposed to air only. Rats from the 4-hour acute dust inhalation were sacrificed after 14 days, whereas rats from the repeat dust exposed groups were terminated on the day after the last exposure. Testis weight, sperm count, and testicular histology were performed for each scheduled killed rat.

For the 4-hour acute dust inhalation study dose-related testicular effects were observed for rats in all exposure groups. Compared to the controls (1.25 g) statistically significantly ($p<0.05$) lower mean testis weights of 0.66, 0.67, 0.58 g were obtained after 14 days in all

groups of dust exposed rats. Also, mean testicular sperm count was reduced to 27.6, 29.2, 15.8, and 2.6 x 10^6 in all dust exposed rats after 14 days in comparison to a mean testicular sperm count of 184.6 x 10^6 in the controls. Histopathological analysis revealed absence of late spermatids in the seminiferous tubules of the lower exposed group (495 mg dust/ m^3). It is reported, that all stages of differentiating spermatids were absent in the highest exposed group (1802 mg dust/ m^3). Also, tubules containing Sertoli cells only and tubules with multinucleated giant cells were prevalent.

Repeat exposure on consecutive days resulted in death of 2 males out of 8 at dust concentrations of 106 mg of PTBBA in air/m^3 and of 7 males out of 8 at dust concentrations of 525 mg of PTBBA in air/m^3. No deaths occurred at the low concentration group. Lower testis weights were reported for the few survivors from the mid and the high exposure groups only, exposures which revealed to be lethal. Lower testicular sperm counts, however, were obtained for all dust exposed groups with 236.5, 188, 93, and 9.7 x 10^6 sperm count/testis in the 0, 12.5, 106, and 525 mg/m^3 exposure groups. From histopathological analysis at necropsy 10 days after the first exposure, there was no apparent effect on spermatogenesis from dust exposure in the low dose group. Absence of late spermatids, presence of multinucleated giant cells, and reduction in spermatogenic cell types were observed in testes from the survivors of the middose group (106 mg/m^3).

A $LOAEC_{testes\ toxicity}$ of 12.5 mg/m^3 PTBBA can be derived from this study based on the findings of a reduction of 21 % in mean number of sperm per testis and of testes weight reduction, hypospermia and degeneration of the seminiferous tubules at the higher exposures.

Studies in humans

Possible testicular effects associated with occupational exposure to PTBBA were investigated in a cohort of 90 male volunteers of a PTBBA producing facility (Whorton et al., 1980, 1981). The control group consisted of 103 volunteers who did not work in the facility and who had not been exposed to any known testicular toxin. The study group of the PTBBA producing facility comprised participants of five different job categories: Operators/Drummers (n=39), Maintenance (n=22), Shipping (n=2), Laboratory (n=4) and Supervisors/Foremen (n=23). Exposures were divided into three different time periods and indexed (with a weighted relative exposure point system) and evaluated for each occupation: from 1954 to 1964 (before the installation of the dust extraction system in use at the time of the study), from 1964 to 1978 (before the initiation of personal protective practices, such as use of respirator, clothing change, shower, etc.) and from 1978 to 1979, when levels at the workplace among operators and drummers ranged from less than 0.1 mg/m^3 to 0.5 mg/m^3. The respirable fraction of airborne dust ranged from 21 to 51 %. An exposure index for each person was calculated based on the relative exposure point values and the amount of time in a given job. Medical evaluations were based on (i) self-administered questionnaire for marital and reproductive history and smoking history, (ii) administered questionnaire for work history and genitourinary medical history, (iii) a brief physical examination of the male genitalia, (iv) venous blood sample for haematology (erythrocyte and leukocyte count) and clinical chemistry (creatinine, blood urea, SGOT, bilirubin, alkaline phosphatase, cholesterol, triglycerides), and serum hormone levels of FSH, LH and testosterone, (v) two semen samples that were analysed for volume, sperm count and sperm morphology. Because of the large range of sperm counts found in healthy men who have not been exposed to chemicals that could influence sperm production, the distribution of sperm counts in a group of subjects was taken as a criterion of possible testicular damage in order to improve the evaluation.

Of the 90 participants 33 had undergone a vasectomy and did not contribute to semen analysis. A total of only 51 of the 90 participants provided at least one semen sample. Thirty-nine men provided a total of two semen samples. Exposure indices were similar between both groups, the semen sample providing men as well as the non semen providing participants. Analysis of the sperm count data of the 51 individuals of the study group (the number of subjects was considered too small to evaluate sperm-count results by job category) yielded a median sperm count of 72 million sperm/ml semen, while that of the control group was 78 million sperm/ml. 8 individuals in the study group (15.7 %) had sperm counts of less than 20 million sperm/ml (e.g. in the sub-fertile range), compared to 7 subjects in the control group. The authors calculated that this difference was not significant and concluded that PT BBA, at the exposures experienced at that plant, had no clinically detectable effect on testicular function of the workers. Also, there were no indications that PTBBA caused infertility in men who took part in this study. No adverse effects on liver and kidney function or on blood composition were observed The levels of the hormones studied were in the normal range in the semen providing and the other participants. To obtain a better statistical analysis of the data from this study, the authors decided that the control group was increased in size by including 232 men who had served as controls in other similar studies (Ross, 1982). Of the group of non-exposed men (then numbering 335), 25 (7.5%) had sperm counts less than 20 million/ml. It is reported, that depending on the process used for statistical analysis, the slight difference between the study subjects and the non-exposed group might or might not have been significant. Closer analysis of the urological-clinical data for the men with oligospermia in the study group of the plant revealed that a multitude of other potential factors, such as orchitis after mumps, testicular hernias and sclerosis of the penis could have been responsible for the reduced sperm density. The urological-clinical data for the control group could not be evaluated to further improve the statistical analysis. The small size of the study group together with the manifold urological findings make the biological significance of the difference from the control group questionable.

4.1.2.9.2 Developmental toxicity

Studies in animals

No data available.

Studies in humans

No data available.

4.1.2.9.3 Summary of toxicity for reproduction

Any hazard assessment for PTBBA with respect to developmental toxicity is not possible since there are no human or experimental data available in the database.

With regard to male fertility, several studies with rats with different routes of application (oral-diet, inhalation, dermal) are available revealing a toxic potential of PTBBA with induction of testicular lesions, spermatotoxic effects and (reversible) infertility already at relatively low dosages/concentrations. Consistently and independent from route of application testes impairment was characterised by lower absolute and relative organ weights, testes atrophy from seminiferous tubular degeneration, with destruction of the germinative

epithelium resulting in disturbance of spermatogenesis and in particular in loss of late spermatids. Concern on possible spermatotoxic effects of PTBBA also in humans can further be derived from a study on occupationally exposed workers providing some indication for slightly higher numbers of individuals with low sperm count (less than 20 million sperm/ml) in exposed participants compared to non-exposed participants.

Any hazard assessment for PTBBA with respect to female fertility is not possible, since there are no data available.

NOAEL/LOAEL values derived from the experimental studies and valid for use for risk assessment are provided in table 4.7.

Table 4.6 NOAEL/LOAEL values from different administration routes for fertility risk characterisation

Route of application	NOAEL/C	LOAEL/C	Reference
Oral	1.6 mg/kg bw/d	7.9 mg/kg bw/d	Hoechst, 1987
Oral/ 90 days	-	6 mg/kg bw/d	Hunter et al., 1965
Dermal/ 7 and 13 weeks	35 mg/kg bw/d	70 mg/kg bw/d	Lu et al., 1987, Cagen et al., 1989
Dermal / 28 days	30 mg/kg bw/d	60 mg/kg bw/d	Shell, 1975
Inhalation/ 4 days (3 days rest) 3 days	-	12.5 mg/m^3	Shell, 1982, Lu et al., 1987

Since a clear-cut toxic potential specifically adverse to male gonads and resulting in impaired male fertility in rats was revealed for PTBBA repeatedly in several studies and consistently across various routes of administration the substance should be classified as a reproductive toxicant T, Repr. Cat 2 and labelled with R 60 (possible risk of impaired fertility). In September 2007 the TC C&L agreed for fertility repr. Cat. 2; R60.

4.1.3 Risk characterisation [9]

4.1.3.1 General aspects

Data on toxicokinetics, metabolism and distribution of 4-tert-butylbenzoic acid after oral, dermal and inhalative uptake in animals and humans are not available. Therefore, the estimation of the extent of absorption is based on physico-chemical data and on results of toxicological investigations.

From physico-chemical properties (water solubility (47.1 mg/l), molecular weight (178.23 g/mol) an octanol-water partition coefficient log Pow of 3.4 and a vapour pressure of of 0.057

[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.

Pa at 20°C) and its physical state (crystalline solid at room temperature) the substance can be assumed to have a probably good oral, dermal and inhalative bioavailability. However, due to the pKa of 4.36, only small amounts of the substance may be present in the non-ionised form at the pH values present in small intestine (pH 4-6 according to TGD). This makes complete absorption from the small intestine unlikely. Toxic effects, which can be observed after acute and subacute oral and dermal application of the substance are indicative of gastrointestinal absorption and dermal absorption, but quantification is not possible. Therefore, absorption via the oral and dermal route is assumed to be 100 % (default-value).

Toxic effects which could be observed after acute and repeated exposure of rats towards particle dusts of PTBBA are indicative of inhalative uptake. However, any quantification is not possible. Therefore, absorption via inhalation is also assumed to be 100 % (default value).

Human data on acute toxicity of 4-tert-butylbenzoic acid are not available. In studies with rats, oral LD50 values of > 550 mg/kg and < 800 mg/kg bw were determined with females being slightly more sensitive than males. Testicular atrophy was produced in male rats exposed to a single dose of 500 mg/kg, and degeneration of the generative cells in the seminiferous tubules were observed. The oral LD50 for mice was determined at 568 mg/kg bw. An inhalation LC50 was not determined but exposure of rats to 1.8 mg dust/l/4 hours resulted in death of 2/6 male and 1/6 female rats indicating a LC 50 of > 1.8 mg/l. Testicular and CNS changes and changes in body weight were already noted at the lowest concentration tested (0.495 mg/l). The assessment of acute dermal toxicity demonstrated great species differences. In rats, a dermal LD50 of about 300 mg/kg resulted when a 30% solution of the substance in DMSO was tested. In rabbits, the dermal LD50 was found to be > 2000 mg/kg when the dry powder was applied. Based on the available data in September 2007 the TC C&L agrred that for acute toxicity the available LC50 for inhalation and the LD50 for dermal application were not sufficient for classification. Only the oral route was then recommended for classification (R22).

Human data on skin or eye irritation caused by 4-tert-butylbenzoic acid are not available. In Draize tests with rabbits the substance did not cause any signs of irritation to the skin and only mild reversible irritation to the eyes of rabbits. Based on these data, the substance is not to be classified as irritant or corrosive, no labelling with R-phases is warranted.

In a Maximization Test (Magnusson Kligman Test) guinea pigs showed no skin reactions after the challenge treatment. Human data on skin sensitization are not available for 4-tert-butylbenzoic acid. Labeling for skin sensitizing properties is not warranted.

No information is available on the effects of repeated exposure in humans. Systemic toxic effects have been observed in animals after repeated inhalation, oral or dermal exposure of 4-tert-butylbenzoic acid.

The target organs for repeat dose toxicity of PTBBA were the central nervous system, liver, kidneys, testes, epididymides, hemopoietic system and the thymus. Regional poliomyelomalacia and responsive gliosis of the spinal cord described in the Shell study (1982) can be associated to the fore and hind limb paralysis and gait abnormalities that was observed in the 11 day-inhalation study at particle concentrations of 106 mg/m³ and above. Increased activity of serum transaminases, speckled, enlarged appearance of the liver were consistent with the liver cell toxicity observed in all repeat-dose studies available. Reduced serum cholesterol levels and fatty vacuolation of liver cells can be assumed to reflect a disturbance of lipid metabolism. The tubular epithelium of the distal cortical convoluted tubules and papillary region (renal pelvis) seemed to be the primary sites of 4-tert-

butylbenzoic acid toxicity. Increased diuresis, hematuria, tubular casts, regenerative epithelium, interstitial inflammation, hyrdronephrosis and hydroureter were associated lesions that can be considered as the death-related cause in the oral study of Hunter et al. (1965). Testicular lesions attributable to 4-tert-butylbenzoic acid occurred in rats exposed via all exposure routes. Similar effects were observed in the studies available, which were characterised by the degeneration of germinal epithelium resulting in disturbance of spermatogenesis at several stages of spermatogenic cells. The presence of multinucleated giant cells in the luminal of seminiferous tubules of testes was indicative for a more chronic process. Corresponding secondary changes were atrophy and inflammatory responses of the epididymides.

Similar lesions in the liver, kidney, male reproductive organs and peripheral blood were identified across all studies regardless of the route of exposure. Neurotoxicity was produced after repeated inhalation and oral administration. No clinical signs of abnormal neurobehaviour or morphological abnormalities of nervous tissues were reported from the dermal study.

Based on the most sensitive adverse effect observed in the studies available the following NOAELs (or LOAELs) for systemic toxicity of 4-tert-butylbenzoic acid were derived: a $NOAEC_{systemic}$ of 5 mg/m³ for inhalation from the 28-day study (HRC, 1995), a LOAEL of 100 ppm (6 mg/kg bw/d) for the oral route from the 90-day study (Hunter et al., 1990), and a LOAEL of 7.5 mg/kg bw/d for the dermal route from the 28-day study (Shell, 1975).

The only indications on respiratory tract effects were seen in the 11 day-inhalation study, where rats exposed to 106 mg/m³ and above showed bright red lungs and a tendency for increase in relative lung weight. Microscopic examination of tissues from the nasal passages, the larynx, trachea and lungs of the respiratory tract were conducted and did not indicate a PTBBA related effect. Samples of the lungs were examined histopathologically in all rats of the 28 day-inhalation study, however, no treatment related effect was observed in the exposed rats. It is concluded from the limited data that repeated inhalation of PTBBA did not cause respiratory tract toxicity. The $NOAEC_{resp}$ for toxic effects on the respiratory tract was 525 mg/m³.

Based on the above data, 4-tert-butylbenzoic acid should be classified “T, R48/23/24/25, Toxic by inhalation, in contact with skin and if swallowed”. The adverse effect levels were far below the guidance values for the classification as harmful. Therefore the currently applied classification should be replaced. In Sepetember 2007 the TC C&L agreed T; R48/23/24/25.

4-tert-Butylbenzoic acid did not induce gene mutations in several Salmonella typhimurium strains.. An *in vitro* micronucleus test with 4-tert-Butylbenzoic acid was weakly positive with metabolic activation in Chinese Hamster V79 cells. An in vivo test on chromosomal aberrations in rats was negative for doses which correspond to the MTD. Oral bioavailability can be asssumed from the physico-chemical data. This is in line with the fact that toxic effects were observed after acute and subacute oral application of low doses of the substance as well as the weak local effects (reduction of mitotic indices) in the *in vivo* chromosomal aberration test. There is sufficient evidence to conclude, that a clastogenic potential of ptBBA observed *in vitro* is unlikely to be expressed in germ cells *in vivo*.

However, due to the positive *in vitro* micronucleus test and the fact that clastogenicity and aneugenicity were not distinguished in this test there is concern for local clastogenic effects and aneugenic effects cannot be excluded. Therefore further testing for clarification is

recommended, preferably a combination of an *in vivo* COMET assay (directly exposed tissue and liver) and a bone marrow micronucleus test.

Several studies with rats applying several routes of application (oral diet, inhalation, dermal) revealed a toxic potential of PTBBA with regard to male fertility. Induction of testicular lesions, spermatotoxic effects and (reversible) infertility have been observed already at relatively low dosages/concentrations. Consistently and independent from route of application testes impairment was characterised by lower absolute and relative organ weights, testes atrophy from seminiferous tubular degeneration, with destruction of the germinative epithelium resulting in disturbance of spermatogenesis and in particular in loss of late spermatids. The following N/LOAEL/C values derived from the various experimental studies are proposed for risk characterisation purposes: $NOAEL_{oral}$ of 1.6 mg/kg bw/d, $NOAEL_{dermal}$ of 30 mg/kg bw/d, and LOAEC 12.5 mg/m^3. Any hazard assessment with respect to female fertility impairment is not possible, since there are no data available.

Concern on possible spermatotoxic effects of PTBBA in men can be derived from a study on occupationally exposed workers providing some indication for slightly higher numbers of individuals with low sperm count (less than 20 million sperm/ml) in exposed participants compared to non-exposed men.

Any hazard assessment for PTBBA with respect to developmental toxicity is not possible since there are no human or experimental data available in the database.

Since a clear-cut toxic potential specifically adverse to male gonads and resulting in impaired male fertility in rats was revealed for PTBBA repeatedly in several studies and consistently across various routes of administration the substance should be classified as a reproductive toxicant T, Repr. Cat 2 and labelled with R 60 (possible risk of impaired fertility). In September 2007 the TC C&L agreed for fertility repr. Cat. 2; R60.

Table 4.7 Summary of effects

Substance name	Inhalation (N(L)OAEL)	Dermal (N(L)OAEL)	Oral (N(L)OAEL)
Acute toxicity	> 1.8 mg dust/l (LC50 rats)	300 mg/kg bw (LD50 rats); > 2000 mg/kg bw (LD50 rabbits)	> 500 - < 800 mg/kg bw (LD50 rats); 568 mg/kg bw (LD 50 mice)
Irritation / corrosivity		Skin: no irritation; eye: mild, reversible irritation	
Sensitization		Skin: not sensitizing in guinea pigs	
Repeated dose toxicity (local)	525 mg/m^3 (NOAEC) 28 d, rats		
Repeated dose toxicity (systemic)	5 mg/m^3 (NOAEC) 28 d, rats	7.5 mg/kg bw/d (LOAEL) 28 d, rats	6 mg/kg bw/d (LOAEL) 90 d, rat
Mutagenicity	*in vitro* weakly positive		
Carcinogenicity	No data	No data	No data
Fertility impairment	12.5 mg/m^3 (LOAEC) rats	30 mg/kg bw/d (NOAEL) rats	1.6 mg/kg bw/d (NOAEL) rats
Developmental toxicity	No data	No data	No data

4.1.3.2 Workers

Introductory remarks

Human exposure of PTBBA (4-tert-butylbenzoic acid) occurs nearly solely during production and further processing of the substance. For occupational risk assessment the MOS approach as outlined in the TGD (Human Health Risk Characterisation, Final Draft) is applied. This occupational risk assessment is based upon the toxicological profile of PTBBA (chapter 4.1.2) and the occupational exposure assessment (chapter 4.1.1.2). The threshold levels identified in the hazard assessment are taken forward to this occupational risk assessment.

This introductory remark specifies the route-specific information on absorption, applies these absorption data to transform the external occupational exposure levels to the corresponding internal body burden, and gives a short introduction to the MOS approach used.

Systemic availability for different routes of exposure

There are no experimental data for PTBBA available which provide information about the absorption after oral, dermal or inhalation exposure. Comparing the N(L)OAELs from the available subacute oral, dermal and inhalation studies (transformed in mg/kg/d) the values are similar. According to the chapter 4.1.2.1 on toxicokinetics, metabolism and distribution the absorption is estimated to be 100% (default values) for oral, dermal and inhalation exposure.

Occupational exposure and internal body burden

In table 4.9 the exposure levels of table 4.1 are summarised and the route-specific and total internal body burdens are identified. Risk assessment for combined exposure requires the calculation of a total internal body burden; to this end the derived route-specific percentages for absorption are used (100% for inhalation and dermal exposure).

Table 4.8 Occupational exposure levels and internal body burden (PTBBA)

Exposure scenario	Inhalation		Dermal contact		Internal body burden		
					Inhalation[(1)]	Dermal[(2)]	Combined
	mg/m³	mg/kg/d	mg/p/d	mg/kg/d	mg/kg/d		
1a Production of PTBBA salts	0.05[(4)]	0.007	42[(3)]	0.6	0.007	0.6	0.607
1b PTBBA used as a chemical intermediate	1.0[(3)]	0.14			0.14		0.74
2. Production of alkyd resins in the polymers industry	0.0625[(3)]	0.001	42[(3)]	0.6	0.001	0.6	0.601

[(1)]based on the assumption of 100% absorption for inhalation and a breathing volume of 10 m³/70 kg per shift
[(2)]based on the assumption of 100% absorption following dermal contact
[(3)] EASE (90 % protection by suitable gloves)
[(4)]Measurement data

MOS Approach

The MOS approach for human risk characterisation is described in detail in the TGD (Human Health Risk Characterisation, Final Draft). The following chapter contains a short introduction to the MOS approach used. The basic principle of the MOS approach is a comparison of scenario-specific MOS values (the relationship between the experimental NOAEL respectively the adjusted starting point and the exposure level) with a reference MOS (product of various assessment factors).

MOS calculation and the adequate starting point

Basically, MOS values are calculated as quotient of a relevant NOAEL from experimental animal testing or human studies and actual workplace exposure levels. In specific situations, the MOS approach requires to convert the original NOAEL into an adequate starting point or corrected NOAEL previously to MOS calculation in order to be directly comparable to the exposure assessment. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental data should be converted to the dose unit of the exposure data. Additionally, possible differences in bioavailability between routes, as well as possible differences in bioavailability between animals and humans should be accounted for the calculation of the corrected NOAEL. If route-specific information on oral and inhalation absorption is not available, the TGD recommends to assume 50% oral absorption and 100% inhalation absorption. For PTBBA, for all exposure routes 100% absorption is assumed (default values).

For occupational risk assessment, the corrected inhalation NOAEC accounts for the difference of the standard respiratory volume (6.7 m³) and the respiratory volume for light activity (10 m³).

MOS values are calculated for different routes of exposure and for different toxicological endpoints. The routes of exposure specifically considered in occupational risk assessment are exposure by inhalation and dermal contact.

In addition, for risk assessment of combined exposure (exposure by inhalation and dermal contact) an adequate internal NOAEL is derived from external NOAELs and specific information on route-specific absorption. For MOS calculation, the adjusted internal starting point is divided by the internal body burden. Depending on route-specific exposure and absorption, inhalation exposure and/or dermal exposure may contribute to the internal body burden. With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with conclusion ii at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice.

Reference MOS

The MOS values calculated have to be compared with a reference MOS. The reference MOS is an overall assessment factor, which is obtained by multiplication of individual assessment factors. The Technical Guidance Document emphasises several aspects which are involved in the extrapolation of experimental data to the human situation. For these assessment factors, default values are recommended. It is important to point out that any relevant substance-specific data and information may overrule the defined default values.

Interspecies extrapolation is based on allometric scaling (factor 4 for rats and factor 2 for rabbits). For remaining interspecies differences the TGD proposes an additional factor of 2.5.

For workers, an adjustment factor for intraspecies differences of 5 is recommended. Based on an evaluation of empirical data by Schneider et al. (2004) it is anticipated that a factor of 5 will be sufficient to protect the major part of the worker population (about 95%).

For chemical substances it is usually expected that the experimental NOAEL will decrease with increasing duration of application. Furthermore, other and more serious adverse effects may appear with prolonged exposure duration. For duration adjustment, a default factor of 6 is proposed for extrapolation from a subacute to chronic exposure. The duration adjustment factor is lower (a factor of 2) for the transition from subchronic experimental exposure to chronic exposure. For PTBBA, N(L)OAELs from studies with variable duration show only little differences: The LOAEL of a 11-day inhalation study was 3.6 mg/kg/d (lowest tested concentration), in a 28-day inhalation study the LOAEL was 4.32 mg/kg/d (NOAEL 1.44 mg/kg/d), in both cases based on liver weight changes. A 28-day dermal rat study showed a LOAEL of 7.5 mg/kg/d (NOAEL 15 mg/g), in a 90-day dermal rat study the LOAEL was 17.5 mg/kg/d (lowest tested dose). Based on these data for extrapolation from a subacute to chronic exposure an adjusted duration factor of 3 is used.

The TGD defines two further adjustment factors (uncertainty in route-to-route extrapolation and dose-response relationship including severity of effect). In specific cases these factors may be different from one.

Comparison of MOS and reference MOS

The MOS values for different toxicological endpoints and different exposure scenarios are compared with the substance- and endpoint-specific reference MOS. MOS values clearly above the reference MOS do not lead to concern, whereas MOS values that are clearly below the reference MOS are cause for concern. There may be various risk-related aspects which are not covered by default assessment factors. These additional qualitative aspects should be carefully considered when performing a risk assessment and should have adequate influence on finding of conclusions.

Critical Exposure Levels

In a parallel procedure, which gives identical but more direct results, the adjusted toxicological starting point is directly divided by the reference MOS. As a result, an exposure level (in mg/m³ or mg/kg/d) is identified, which may serve as a direct trigger for decisions when compared with the occupational exposure levels. In the context of this risk assessment report this trigger value is called "critical exposure level". Concern will be expressed for scenarios with occupational exposure levels higher than the relevant "critical exposure level".

4.1.3.2.1 Acute toxicity

Human data regarding the acute toxicity of PTBBA are not available. In studies with rats, oral LD50 values of > 550 mg/kg and < 800 mg/kg were detected. An inhalation LC50 was not determined but exposure of rats to 1,802 mg dust per liter over 4 hours resulted in death in 2/6 male and 1/6 female rats.

Inhalation exposure

For risk assessment of acute inhalation toxicity (8-hour exposure) data on PTBBA-induced lethality are considered less relevant than the results from a 5-day inhalation study, where sublethal concentrations have been tested. There at the highest tested concentration of ~15 mg/m^3 neither clinical effects nor bodyweight or organ weight changes were reported.

This experimental value serves as starting point for acute inhalation toxicity without further adaptation.

For the identification of the reference MOS, (1) an adjustment factor of 2.5 for interspecies differences (the factor for allometric scaling is already implicitly applied) and (2) intraspecies differences for workers (factor of 5) are applied. Thus the reference MOS calculates to 12.5 (2.5 • 5). The critical inhalation exposure at the workplace is identified as 1.2 mg/m^3 (15 / 12.5).

There is no concern for scenario 1 and 2 (see table 4.10). Peak exposure levels (e. g. 15-min) are not available.

Conclusion: ii

Dermal contact

In rats, a dermal LD50 of approximately 300 mg/kg resulted when a 30% substance solution in DMSO was tested. In rabbits the dermal LD50 was found to be >2,000 mg/kg when the dry powder was applied.

For assessing the acute dermal toxicity of PTBBA a subacute 28 day rat study is taken (for more details see chapter 4.1.2.6.1 and below under repeated dose toxicity after dermal contact). The LOAEL of 7.5 mg/kg/d based on liver weight increases of female rats is taken for the risk assessment of acute dermal toxicity and serves as starting point.

To calculate the reference MOS (1) an interspecies factor of 4 • 2.5 (rat) and (2) an intraspecies factor of 5 is used. No specific factor is taken to extrapolate from the LOAEL to a possible NOAEL, because this 28-day LOAEL might be a clear NOAEL for a shorter period

of exposure. Alltogether the reference MOS calculates to 50 (4 • 2.5 • 5) the corresponding critical exposure level calculates to 0.15 mg/kg/d (7.5 / 50).

For acute toxicity (liver weight increases) the MOS approach indicates concern for both dermal exposure scenarios, see table 4.10.

Conclusion: iii

Combined exposure

The LOAEL of 7.5 mg/kg/d from the 28-day dermal rat study is taken for the risk assessment of combined toxicity after acute exposure.

The absorption after dermal uptake of PTBBA is calculated with the default of 100%, thus the internal starting point corresponds the LOAEL of 7.5 mg/kg/d.

The reference MOS calculates to 50 (the same derivation than for the assessment of acute dermal contact, see above) the corresponding internal critical exposure level calculates to 0.15 mg/kg/d (7.5 / 50), see table 4.10. Since for dermal exposure concern is given, for combined exposure concern is expressed as well.

Conclusion: iii

Table 4.9 Acute toxicity, systemic effects

	Inhalation			Dermal			Combined Exposure		
Starting point for MOS calculation	15 mg/m^3			7.5 mg/kg/d			7.5 mg/kg/d (internal)		
Reference MOS	12.5			50			50		
Critical exposure level	1.2 mg/m^3			0.15 mg/kg/d (external)			0.15 mg/kg/d (internal)		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/kg/day)	MOS	Conclusion	Exposure (mg/kg/day)	MOS	Conclusion
1a. Production of PTBBA salts	0.05	300	ii	0.6	12.5	iii	0.607	12.3	iii[(1)]
1b. PTBBA used as a chemical intermediate	1.0	15	ii				0.74	10.1	iii[(1)]
2. Production of alkyd resins in the polymers industry	0.0625	240	ii	0.6	12.5	iii	0.601	12.5	iii[(1)]

[(1)]conclusion iii already results from dermal exposure

4.1.3.2.2 Irritation and corrosivity

Skin, Eye

Human data on skin or eye irritation caused by PTBBA are not available. In Draize tests with rabbits the substance did not cause any signs of irritation to the skin and only mild reversible irritation to the eyes of rabbits. The observed effects are not considered sufficient for classification. There is no concern for dermal or eye irritation at the workplace.

Conclusion: ii

Respiratory tract

No local effects from acute or repeated dose tests are described. For further information see also under RDT, local effects.

Conclusion: ii

4.1.3.2.3 Sensitisation

Skin

Human data on skin sensitisation are not available for PTBBA. In a Maximisation Test (Magnusson Kligman Test) guinea pigs showed no skin reactions after the challenge treatment. No concern will be expressed for the endpoint skin sensitisation.

Conclusion: ii

Respiratory tract

No information on the sensitising potential of the substance at the respiratory tract is available. For the time being a valid study to investigate respiratory sensitisation in experimental animals cannot be recommended. However, PTBBA is not suspected to be a potent respiratory sensitiser in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no concern with respect to respiratory sensitisation at the workplace.

Conclusion: ii

4.1.3.2.4 Repeated dose toxicity

Local effects (inhalation, dermal)

No local effects are described from the different inhalation and/or dermal studies with PTBBA at rats.

A concentration of 525 mg/m^3 PTBBA during a time period of 7 days (4 days exposure, 3 days rest and another 3 days exposure) did not result in local effects at rats, whereas systemic effects were seen at 12.5 mg/m^3. Additionally dermal exposure to 140 mg/kg/d over a time period of 90 days did not cause irritation to dermal exposure sites, whereas systemic effects

occured with the lowest tested dose of 17.5 mg/kg/d. There is no concern regarding local effects after dermal or inhalation exposure.

Conclusion: ii

Systemic effects

No information on the effects in humans after repeated exposure to PTBBA is available.

Inhalation exposure

Some subacute inhalation animal studies (one 5-day study, one 11-day study, and one 28-day study) have been performed with PTBBA. In these inhalation tests liver weight changes were the most sensitive parameter (at concerntrations of 15 mg/m^3), a reduction of testes weight occured at 106 mg/m^3. The 28-day inhalation study (see chapter 4.1.2.6.1) serves as key study to assess systemic risks by inhalation.

Rats were exposed to PTBBA concentrations of 1.5, 5, and 15 mg/m^3 for 6 hours per day, 5 days per week for 4 weeks. Based on higher liver weights of females at the high dose, the systemic NOAEC was derived as 5 mg/m^3.

The experimental NOAEC of 5 mg/m^3 is (1) adapted by a factor of 6/8 to account for differences between the experimental inhalation duration of 6 hours per day and the average working day of 8 hours per day, and (2) is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. This results in an adjusted inhalation starting point of 2.5 mg/m^3 (5 • 6/8 • 6.7/10).

For the identification of the reference MOS adjustment factors for interspecies and intraspecies differences, and for differences in frequency of duration are applied. For (1) interspecies differences the default factor is 2.5 (the factor for allometric scaling is already implicitly applied), for (2) intraspecies differences (workers) the default factor is 5. A (3) reduced duration adjustment factor of 3 is used (for detailed explanation see above under chapter MOS Approach). Thus the reference MOS calculates to 37.5 (2.5 • 5 • 3). The critical inhalation exposure at the workplace is identified as 0.067 mg/m^3 (2.5 / 37.5).

The shift average values for inhalation are reported as 0.05 (production of PTBBA salts, scenario 1a) and 1.0 mg/m^3 (PTBBA used as a chemical intermediate, scenario 1b) and 0.0625 mg/m^3 for production of alkyd resins in the polymers industry. The exposure level of scenario 1b is significantly higher than the critical inhalation exposure of 0.067 mg/m³. Concern is expressed for this scenario. Scenario 1a and 2 are just out of concern. For corresponding MOS values see table 4.11.

Conclusion: iii

Dermal contact

Two dermal studies (one subacute and one subchronic study) are available. The 90-day rat study showed a LOAEL of 17.5 mg/kg/day at the lowest tested dose, the LOAEL of the 28-day study was 7.5 mg/kg/day. For assessing the dermal toxicity after dermal contact the subacute 28-day rat study is taken. In this study 8 male and 8 female rats received 0, 7.5, 15, 30 and 60 mg/kg/day PTBBA topically on the skin. Dose related significant increases in absolute and relative liver weights were seen in female rats of all dose groups and in male rats exposed to 15 mg/kg/day and above. Histopathology of the testes revealed a degeneration of

germinal epithelium in males exposed to 60 mg/kg bw/d. The LOAEL was 7.5 mg/kg/day based on the liver weight increases of female rats.

Starting point for the assessment of dermal toxicity after repeated exposure is the LOAEL of 7.5 mg/kg/day.

For the calculation of the reference MOS the following assessment factors are taken: (1) a factor of 3 to extrapolate from the LOAEL to a possible NAEL, (2) a factor of 4 x 2.5 (rat) for interspecies and (3) a factor of 5 for intraspecies differences. Additionally (4) a reduced duration factor of 3 is used (see above under chapter "MOS Approach"). Alltogether the reference MOS calculates to 450 (3 • 4 • 2.5 • 5 • 3) the corresponding critical exposure level calculates to 0.017 mg/kg /day (7.5 / 450).

The calculated exposure values for dermal contact are reported as 0.6 mg/kg /day as well for production of PTBBA salts and PTBBA used as a chemical intermediate (scenario 1) as for production of alkyd resins in the polymers industry (scenario 2). These values are significantly higher than the critical dermal exposure level of 0.017 mg/kg /day. Concern is expressed for both scenarios. For corresponding MOS values see table 4.11.

Conclusion: iii

Combined exposure

For both exposure scenarios, there is concern for both routes of exposure. To assess the combined situation, risks of both pathways can be added and reach automatically concern. Thus no specific calculation for PTBBA is done for combined exposure after repeated contact.

Conclusion: iii

Table 4.10 Repeated dose toxicity, systemic effects

	Inhalation			Dermal			Combined Exposure		
Starting point for MOS calculation	2.5 mg/m^3			7.5 mg/kg/d			no specific calculation (see text)		
Reference MOS	37.5			450			-		
Critical exposure level	0.067 mg/m^3			0.017 mg/kg/d (external)			-		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/kg/day)	MOS	Conclusion	Exposure (mg/kg/day)	MOS	Conclusion
1a. Production of PTBBA salts	0.05	50	ii	0.6	12.5	iii	0.607	-	iii(1)
1b. PTBBA used as a chemical intermediate	1.0	2.5	iii				0.74		iii(1)
2. Production of alkyd resins in the polymers industry	0.0625	40	ii	0.6	12.5	iii	0.601	-	iii(1)

4.1.3.2.5 Mutagenicity

PPTBBA did not induce gene mutations in Salmonella and was negative in an *in vivo* chromosomal aberration test with rats for doses which correspond to the MTD, however a weak reduction of mitotic indices was observed at 24 h sampling in females. An *in vitro* micronucleus test with 4-tert-Butylbenzoic acid was weakly positive with metabolic activation in Chinese Hamster V79 cells.

Assuming oral bioavailability of 4-tert-butylbenzoic acid, there is sufficient evidence to conclude, that a clastogenic potential of 4-tert-butylbenzoic acid observed *in vitro* is unlikely to be expressed in germ cells *in vivo.*

However, due to the positive *in vitro* micronucleus test and the fact that clastogenicity and aneugenicity were not distinguished in this test, further testing for clarification is recommended (see chapter 4.1.2.7).

Conclusion: i

4.1.3.2.6 Carcinogenicity

At present, the carcinogenic potential of PTBBA has not been examined in human population and no animal studies have been conducted. No conclusion can be drawn on the potential of carcinogenicity.Data from mutagenicity testing give no clear answer on genotoxic properties of 4-tert-butylbenzoic acid. Since there is no indication from case reports, and taking into account that 4-tert-butylbenzoic acid has no distinct mutagenic properties, at present no concern for workers with regard to carcinogenicity of 4-tert-butylbenzoic acid is expressed.

Conclusion: ii

4.1.3.2.7 Toxicity for reproduction

Effects on fertility

PTBBA shows a toxic potential to male fertility in several studies with rats after inhalation, dermal or oral route of exposure. The possible spermatotoxic effects of 4-tert-butylbenzoic acid seem to be relevant for humans, as a study on occupationally exposed workers with 4-tert-butylbenzoic acid provides some indication for a slightly higher number of individuals with low sperm count.

An oral one-generation rat study with 4-tert-butylbenzoic acid focussing on male fertility is available. Additional information results from other subacute or subchronic studies, where effects on testes were observed. In an 11-day inhalation study a decrease of sperm count occured at 12.5 mg/m^3, and lower testes weights were found at 106 mg/m^3. A reduced weight of testes was also reported from a 28-day dermal rat study at doses of 60 mg/kg/day 4-tert-butylbenzoic acid.

For occupational risk assessment of fertility impairment the oral one-generation rat study (Hoechst, 1987, see also chapter 4.1.2.9.1) is taken. Ten Wistar rats per group were fed diets

containing 0, 20, 100, or 500 ppm PTBBA for a period of 70 days before starting with mating trials. This corresponds to ≈ 1.6 (20 ppm), 7.9 (100 ppm), and 41 (500 ppm) mg/kg/d. A significant reduction of fertility, a reduction of testes weights and histopathological changes was observed at the high dose of 41 mg/kg/day. At the middle dose (7.9 mg/kg/day) a (slight) reduction of fertility was seen, but no histopathological changes. A NOAEL of 1.6 mg/kg/day 4-tert-butylbenzoic acid is derived from this study.

Internal starting point

The absorption after oral uptake of PTBBA is calculated with the default of 100%, thus the internal starting point corresponds to the NOAEL of 1.6 mg/kg/day.

Inhalation exposure

Calculating with 100% absorption after inhalation, the internal dose is identical to the external inhalatory dose. The dose of 1.6 mg/kg/day is (1) divided by a factor of 0.38 m^3/kg (rat breathing volume during 8 hours) and (2) is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. This results in an inhalative starting point of 2.8 mg/m^3 (1.6 • 1/0.38 • 6.7/10).

For the identification of the reference MOS (1) the interspecies factor of 2.5 for remaining differences is multiplied with (2) the intraspecies factor of 5. No further factor (e.g. addressing the severity of this endpoint) is taken, since there is a factor of about 5 between the NOAEL and the dose where the first fertility effects (but no histopathological changes) were observed. This results in a reference MOS of 12.5 (5 • 2.5). The corresponding critical exposure level calculates to 0.22 mg/m^3 (2.8 / 12.5).

Concern is expressed for scenario 1b, see also table 4.12.

Conclusion: iii

Combined exposure

The internal starting point of 1.6 mg/kg/d is divided by the reference MOS of 50 (the reference MOS for internal and dermal exposure is identical). The corresponding critical internal exposure level calculates to 0.03 mg/kg/d (1.6 / 50). Conclusion iii is reached for all exposure scenarios. Because of the available route-specific conclusions, there is no specific concern for combined exposure.

Conclusion: iii

Table 4.11 Fertility, systemic effects

	Inhalation			Dermal			Combined Exposure		
Starting point for MOS calculation	2.8 mg/m^3			1.6 mg/kg/d			1.6 mg/kg/d (internal)		
Reference MOS	12.5			50			50		
Critical exposure level	0.22 mg/m^3			0.03 mg/kg/d (external)			0.03mg/kg/d (internal)		
	Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/kg/day)	MOS	Conclusion	Exposure (mg/kg/day)	MOS	Conclusion
1a. Production of PTBBA salts	0.05	56	ii	0.6	2.7	iii	0.607	2.6	iii(1)
1b. PTBBA used as a chemical intermediate	1.0	2.8	iii				0.74	2.2	iii(1)
2. Production of alkyd resins in the polymers industry	0.0625	45	ii	0.6	2.7	iii	0.601	2.7	iii(1)

(1)conclusion iii already results from inhalation and dermal exposure

Developmental toxicity

A risk assessment for 4-tert-butylbenzoic acid with respect to developmental toxicity is not possible since no human or experimental data are available.

Since marked effects on testes and male fertility of adults have been observed for 4-tert-butylbenzoic acid, effects for the developmental period can not be ruled out. This results in asking for further testing of developmental toxicity for 4-tert-butylbenzoic acid. However, an alternative approach could be, to add to the NOAEL for fertility effects an extra assessment factor to cover the uncertainty with regard to adult versus foetus sensitivity. For the size of such assessment factor there is no scientific justification given until now.

For pragmatic reasons the following approach regarding developmental toxicity is chosen: Conclusion I (on hold for further testing of developmental toxicity) is expressed keeping in mind that due to the low critical exposure level for systemic effects after repeated exposure (≈ 0.07 mg/m^3) which is about a factor of 3 lower than the critical exposure level for fertility effects (0.22 mg/m^3) risk reduction measures will be implemented, which could also cover risks regarding developmental toxicity.

Conclusion: i (on hold)

4.1.3.2.8 Summary of risk characterisation for workers

The toxicological profile of 4-tert-butylbenzoic acid is characterised by the toxicological effects after acute and repeated exposure. The main target organs are liver, kidneys, the central nervous systemand male reproductive organs. Table 4.13 indicates the toxicological endpoints of concern for 4-tert-butylbenzoic acid. There is concern for acute toxicity, repeated dose toxicity and male fertility. For mutagenicity conclusion i is expressed, for developmental toxicity the conclusion i is set on hold.

Table 4.12 Endpoint-specific risk assessment for workers

Toxicological endpoints		General conclusion
Acute toxicity	inhalation	ii
	dermal	iii
	combined	iii[(1)]
Irritation/ Corrosivity	dermal	ii
	eye	ii
	acute respiratory tract	ii
Sensitisation	skin	ii
	respiratory	ii
Repeated dose toxicity	local, inhalation	ii
	local, dermal	ii
	systemic, inhalation	iii
	systemic, dermal	iii
	systemic, combined	iii [(1)]
Mutagenicity		i
Carcinogenicity	inhalation	ii
	dermal	ii
	combined	ii
Fertility impairment	inhalation	iii
	dermal	iii
	combined	iii[(1)]
Developmental toxicity	inhalation	i (on hold)
	dermal	i (on hold)
	combined	i (on hold)

[(1)]conclusion iii already results from inhalative and/or dermal exposure, therefore no specific concern for the combined exposure scenario is indicated

For this risk assessment animal studies for all three exposure pathways were available. For oral, dermal, and inhalation absorption a percentage of 100% is assumed as default value. Route-specific data (oral, dermal, inhalation) support this assumption.

With respect to effects in the airways after repeated exposure, inhalation exposure levels of 4-tert-butylbenzoic acid should be controlled to values in the range of 0.067 mg/m^3 (critical exposure level of systemic effects after repeated exposure). In doing so, inhalation risks from

other endpoints, especially risks of adverse fertility effects (critical exposure level: 0.22 mg/m^3), as well as possible risks by developmental toxicity are similarly and effectively be mitigated too.

Special attention should be given to skin contact. From the risk assessment there is indication that repeated dermal exposure at the workplace to 4-tert-butylbenzoic acid may not exceed a daily exposure of 0.017 mg/kg/day or 1.2 mg/person/day. In doing so, dermal risks from other endpoints especially risks of adverse fertility effects and possible risks of developmental toxicity (critical exposure level 0.03 mg/kg/day or 2.1 mg/person/day), as well as risks by acute toxicity (critical exposure level 0.15 mg/kg/day or 10.5 mg/person/day) are similarly and effectively be mitigated too.

Tables 4.14 (inhalation) and 4.15 (dermal contact) visualize the risk profile of 4-tert-butylbenzoic acid. According to the specific arrangement of exposure scenarios and critical exposure levels for different toxicological endpoints you will find the relatively high risks in the left upper corner, the relatively low risks in the bottom right corner of the tables. As you can see in the tables the critical exposure levels for repeated dose toxicity show the lowest values.

Table 4.13 Ranking of health risks for workers (inhalation)

Exposure scenario	Exposure level in mg/m³	Repeated dose toxicity, systemic	Fertility impairment	Acute toxicity systemic
		Critical exposure level in mg/m^3		
		0.067	0.22	1.2
1b. PTBBA used as a chemical intermediate	1.0	iii	iii	ii
2. Production of alkyd resins in the polymers industry	0.0625	ii	ii	ii
1a. Production of PTBBA salts	0.05	ii	ii	ii

Table 4.14 Ranking of health risks for workers (dermal contact)

Exposure scenario	Exposure level in mg/kg/d	Repeated dose toxicity, systemic	Fertility impairment	Acute toxicity systemic
		Critical exposure level in mg/kg/d		
		0.017	0.03	0.15
1. Production of PTBBA salts and PTBBA used as a chemical intermediate	0.6	iii	iii	iii
2. Production of alkyd resins in the polymers industry	0.6	iii	iii	iii

4.1.3.3 Consumers

There is no information for the use of consumer products containing PTBBA in the BfR product database and other available European databases.

But there is information that dermal exposure of humans to 4-tert-butylbenzoic acid may occur due to migration from sex toys (Nilsson et al., 2006). The worst case estimation results in an external dermal exposure of up to 2.5 µg/kg bw/d.

Acute toxicity

Dermal

Following the exposure assessment, consumers are not exposed to PTBBA in the range of hazardous doses which can be derived from dermal toxicity figures based on animal LD50 values. Therefore, the substance is of no concern in relation to dermal toxicity.

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

Irritation / corrosivity

In Draize tests with rabbits the substance did not cause any signs of irritation to the skin of rabbits.

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

Sensitisation

PTBBA did not produce dermal sensitization in guinea pigs in a maximization test.

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

Repeated dose toxicity

Dermal exposure

In a 28-day dermal study (Shell, 1975) groups of male and female rats received 7.5, 15, 30 and 60 mg/kg bw/d PTBBA topically on shaved skin. Dose-related significant increases in absolute and relative liver weights were seen in female rats of all dose groups and in male rats exposed to 15 mg/kg/d and above. Increased relative weights of kidneys were observed in two

top doses of female rats, and decrease in relative and absolute testes weights were determined for male rats receiving 60 mg/kg/d. Histopathology of the testes revealed a degeneration of germinal epithelium in males exposed to 60 mg/kg/d. The risk characterisation for dermal exposure (systemic effects) is based on the LOAEL of 7.5 mg/kg bw/d from this study.

In a subchronic dermal toxicity study (Cagen et al., 1989; Lu et al., 1989) aqueous solutions (1 ml/kg bw) containing the diethanolamine salt of PTBBA at a ratio of 1.7:1.0 were applied to F344 rats resulting in exposures of 17.5, 35, 70, or 140 mg/kg bw/d PTBBA. Exposure-related pathologic changes of the two highest doses were confined to three organ systems: cytoplasmic vacuolisation in the liver, pallor, dilatation, degeneration and regeneration of distal convoluted tubular epithelium, tubular casts, interstitial nephritis and papillary necrosis of the kidneys; and moderate to severe diffuse tubular degeneration with absence of late spermatides, reduced number of spermatogenic cell types, and giant cell formation in the testes. Liver cell vacuolisation was also evident in female rats treated with 17.5 mg/kg bw/d (LOAEL) and 35 mg/kg bw/d. In male rats exposed to ≥70 mg/kg PTBBA the testicular effects were marked, no effects were detected in males exposed to the lower doses.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to the TGD. The findings of all studies are not contradictory.

- uncertainty arising from the variability in the experimental data

For dermal exposure of consumers (systemic effects) the LOAEL of 7.5 mg/kg bw/d from the 28-day study on rats will be used for risk characterisation.

There are no reasons to assume a special extent of uncertainty which has to be taken into account.

- intra- and interspecies variation

Data on toxicokinetics of the substance are not available. Therefore, a calculation of the intraspecies and interspecies variability by applying modern approaches is not possible.

- the nature and severity of the effect

The 28-day dermal study on rats showed dose-related significant increases in absolute and relative liver weights in female rats of all dose groups and in male rats exposed to 15 mg/kg bw/d and above. Increased relative weights of kidneys were observed in two top doses of female rats, and decreases in relative and absolute testes weights were determined.

There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, hence they are of relevance for humans.

- differences in exposure (route, duration, frequency and pattern)

For dermal risk characterisation a rat study is used which follows dermal exposure. Thus, the estimated dermal exposure is compared with the dermal LOAEL. There are no reasons to assume a special concern from this procedure.

- the human population to which the quantitative and/or qualitative information on exposure applies

Following the exposure scenario there is no reason to assume a special risk for elderly.

MOS for the dermal exposure scenario

The external dermal exposure of humans due to migration from sex toys has been estimated to be 0.0025 mg/kg bw/d. The margin of safety between the

exposure level of	0.0025 mg/kg bw/d

and the

dermal LOAEL of	7.5 mg/kg bw/d

is judged to be sufficient even taking into account that a LOAEL is used.

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

Mutagenicity

4-tert-Butylbenzoic acid did not induce gene mutations in Salmonella. An in vitro micronucleus test with 4-tert-Butylbenzoic acid was weakly positive with metabolic activation. An in vivo test on chromosomal aberrations in rats was negative for doses which correspond to the MTD. There is sufficient evidence to conclude, that the genotoxic potential of ptBBA observed in vitro is unlikely to be expressed in germ cells in vitro. However, local genotoxic effects on directly exposed tissues cannot be excluded. Due to the C&L decision (September 2007) for reprotoxicity Cat. 2; R60 there is a need for a ban of the substance in consumer products according Directive 76/769 and further testing for local genotoxicity is not appropriate.

Conclusion (i) On hold for further testing regarding local genotoxic effects.

Carcinogenicity

The carcinogenic potential of 4-tert-butylbenzoic acid has not been examined. Thus, at present no conclusion can be drawn on the carcinogenic potential. However, if further mutagenicity testing will be required, their results have to be taken into considerationss

Conclusion (ii) There is at present no need for further information and/or testing or for

risk reduction measures beyond those which are being applied already

Toxicity for reproduction

Effects on fertility

Several studies with rats via different routes of application (oral diet, inhalation, dermal) revealed the potential of PTBBA to impair male fertility. Induction of testicular lesions, spermatotoxic effects and (reversible) infertility already at relatively low dosages/ concentrations have been observed. Consistently and independent from route of application testes impairment was characterised by lower absolute and relative organ weights, testes atrophy from seminiferous tubular degeneration, with destruction of the germinative epithelium resulting in disturbance of spermatogenesis and in particular in loss of late spermatids. The following NOAEL values derived were derived from the experimental studies: NOAELoral of 1.6 mg/kg bw/d (Hoechst, 1987), NOAELdermal of 35 mg/kg bw/d (Lu et al., 1987; Cagen et al., 1989), and NOAEC 106 mg/m3 (Lu et al., 1987).

Concern on possible spermatotoxic effects of PTBBA to men can further be derived from a study on occupationally exposed workers providing some indication for slightly higher numbers of individuals with low sperm count in exposed participants compared to non-exposed males.

In September 2007 the TC C&L agreed on repr. Cat.2;R60.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- overall confidence in the database

The data taken into account for performing the risk characterization have been evaluated with regard to their reliability, relevance and completeness according to the TGD. No studies according to internationally acknowledged guidelines were presented.

There are no reasons to assume limited confidence.

- uncertainty arising from the variability in the experimental data

The oral NOAEL for fertility of 1.6 mg/kg bw/d from the rat study by Hoechst (1987) is considered to be the appropriate value for risk characterisation.

- intra- and interspecies variation

Data on toxicokinetics of the substance are not available. Therefore, a calculation of the intraspecies and interspecies variability by applying modern approaches is not possible.

- the nature and severity of the effect

The effects are considered to be severe health effects.

It can be assumed that the effects shown in the animal experiments are relevant for men. A study on occupationally exposed workers provided some indication for slightly higher numbers of individuals with reduced sperm count in PTBBA exposed participants.

- differences in exposure (route, duration, frequency and pattern)

The estimated dermal exposure is compared with a dermal NOAEL from a rat study. There are no reasons to assume a special extent of uncertainty which has to be taken into account.

- the human population to which the quantitative and/or qualitative information on exposure applies

Any hazard assessment with respect to female fertility impairment is not possible, since there are no data available.

- other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for the dermal exposure scenario

The external dermal exposure has been estimated to be up to 0.0025 mg/kg bw/d. The margin of safety between the

exposure level of 0.0025 mg/kg bw/d

and the

dermal NOAEL of 35 mg/kg bw/d

is judged to be sufficient.

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.

Developmental toxicity

Any hazard assessment for PTBBA with respect to developmental toxicity is not possible since no human or experimental data are available. But the decision of the TC C&L in September 2007 for repr. Cat. 2; R60 is a driver for limiting the substance in consumer products by effective measures on the protection of consumers for concern on developmental toxicity.

Conclusion (i) On hold for further developing toxicity testing in the light of the risk reduction strategy.

4.1.3.3.1 Summary of risk characterisation for consumers

Due to the presence of ptBBA in consumer products and the decision of the C&L meeting in September 2007 for classifying PTBBA as repr. Cat2, R60 there is a need for restricting the substance. These measures will protect consumers also for possible effects on mutagenicity as well on developmental toxicity, therefore for both the conclusion (i) is on hold in the light of risk reduction strategy.

4.1.3.4 Humans exposed via the environment

4.1.3.4.1 Exposure via air

According to the calculations (cf. 4.1.1.4) an intake of PTBBA via air is negligible.

4.1.3.4.2 Exposure via food and water

Worst-case calculations for the scenario "Use as stabilizer in PVC" resulted in a total daily dose of 0.00038 mg/kg bw/d at the local level (cf. 4.1.1.4). For the regional scenario a total daily dose of $5.8 \cdot 10^{-6}$ mg/kg bw/d was calculated.

Local exposure near point source

Repeated dose toxicity
In a 90-day study rats were orally administered to diets containing doses of 0, 100, 316, 1000, 3160 and 10000 ppm of PTBBA (calculated intake 6, 21, and 75 mg/kg bw/d for males, 8, 27, 89 mg/kg bw/d for females, no calculation on the top two doses) (Hunter et al., 1965). The study showed renal tubular necrosis and papillary necrosis in treated male and female rats of all dose groups as well as a testes atrophy which was related to degenerated epithelium of seminiferous tubules. Thus, the value of 6 mg/kg bw/d was derived as LOAEL for adverse effects after chronic exposure.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. The findings of all studies are not contradictory.

- uncertainty arising from the variability in the experimental data

For oral exposure to PTBBA via the environment the LOAEL of 6 mg/kg bw/d derived from the 90-day study on rats will be used for risk characterisation. There are no reasons to assume a special extent of uncertainty which has to be taken into account.

- intra- and interspecies variation

Data on toxicokinetics of the substance are not available. Therefore, a calculation of the intraspecies and interspecies variability by applying modern approaches is not possible.

- the nature and severity of the effect

The subchronic study on rats fed with PTBBA diets showed renal tubular necrosis and papillary necrosis in treated male and female rats of all dose groups as well as a testes atrophy.

There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, hence they are of relevance for humans.

MOS for the local exposure scenario

The local exposure has been estimated to be 0.00038 mg/kg bw/d. The margin of safety between the

exposure level of 0.00038 mg/kg bw/d

and the

oral LOAEL of 6 mg/kg bw/d

is judged to be sufficient

even taking into account that a LOAEL is used. Thus, regarding repeated dose effects the substance is of no concern in relation to indirect exposure via the environment.

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

Mutagenicity

4-tert-Butylbenzoic acid did not induce gene mutations in Salmonella. An in vitro micronucleus test with 4-tert-Butylbenzoic acid was weakly positive with metabolic activation. An in vivo test on chromosomal aberrations in rats was negative for doses which correspond to the MTD. There is sufficient evidence to conclude, that a clastogenic potential of ptBBA observed in vitro is unlikely to be expressed in germ cells in vivo.

However, due to the positive *in vitro* micronucleus test and the fact that clastogenicity and aneugenicity were not distinguished in this test there is concern for local clastogenic effects and aneugenic effects cannot be excluded. Therefore further testing for clarification is recommended, preferably a combination of an *in vivo* COMET assay (directly exposed tissue and liver) and a bone marrow micronucleus test.

The need for a further in vivo testing to evaluate genotoxicity should be revisited in the light of the risk reduction strategy.

Conclusion (i) On hold for further testing on genotoxic effects in vivo.

Carcinogenicity

The carcinogenic potential of 4-tert-butylbenzoic acid has not been examined. Thus, at present no conclusion can be drawn on the carcinogenic potential. However, positive results of further in vivo mutagenicity testing should be taken into considerations for test strategies on carcinogenicity.

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

Reproductive toxicity

Fertility
Several studies with rats via different routes of application (oral diet, inhalation, dermal) revealed the potential of PTBBA to impair male fertility. Induction of testicular lesions, spermatotoxic effects and (reversible) infertility already at relatively low dosages/ concentrations have been observed. Consistently and independent from route of application testes impairment was characterised by lower absolute and relative organ weights, testes atrophy from seminiferous tubular degeneration, with destruction of the germinative epithelium resulting in disturbance of spermatogenesis and in particular in loss of late spermatids. The $NOAEL_{oral}$ of 1.6 mg/kg bw/d was derived from the diet rat study (Hoechst, 1987, cf. 4.1.2.9.1).

Concern on possible spermatotoxic effects of PTBBA to men can further be derived from a study on occupationally exposed workers providing some indication for slightly higher numbers of individuals with low sperm count in exposed participants compared to non-exposed males.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- overall confidence in the database

The data taken into account for performing the risk characterization have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. No studies according to internationally acknowledged guidelines were presented.

There are no reasons to assume limited confidence.

- uncertainty arising from the variability in the experimental data

The oral NOAEL for fertility of 1.6 mg/kg bw/d from the rat study by Hoechst (1987) is considered to be the appropriate value for risk characterisation. There are no reasons to assume a special extent of uncertainty which has to be taken into account.

- intra- and interspecies variation

Data on toxicokinetics of the substance are not available. Therefore, a calculation of the intraspecies and interspecies variability by applying modern approaches is not possible.

- the nature and severity of the effect

The effects are considered to be severe health effects.

It can be assumed that the effects shown in the animal experiments are relevant for men. A study on occupationally exposed workers provided some indication for slightly higher numbers of individuals with reduced sperm count in PTBBA exposed participants.

- the human population to which the quantitative and/or qualitative information on exposure applies

Any hazard assessment with respect to female fertility impairment is not possible, since there are no data available.

MOS for the local exposure scenario

The local exposure has been estimated to be 0.00038 mg/kg bw/d. The margin of safety between the

exposure level of 0.00038 mg/kg bw/d

and the

oral NOAEL of 1.6 mg/kg bw/d

is judged to be sufficient.

In addition, the decision of the TC C&L in September 2007 for repr. Cat. 2; R60 for 4-tert-butylbenzoic acid has the consequence that restricting approaches are needed.

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

Developmental toxicity

Any hazard assessment for PTBBA with respect to developmental toxicity is not possible since there are no human or experimental data available. However, the decision of the C&L meeting in September 2007 with repr. Cat. 2, R60 has the consequences that limiting approaches of the substance will be initiated. Therefore the need for a test to evaluate developmental toxicity should be revisted in the light of the risk reduction strategy.

Conclusion (i) On hold for further testing waiting for the outcome of risk reduction strategy that further possible measures are needed.

Regional exposure

Repeated dose toxicity

MOS for the regional exposure scenario

The regional has been estimated to $5.8 \cdot 10^{-6}$ mg/kg bw/d. The margin of safety between the

exposure level of $5.8 \cdot 10^{-6}$ mg/kg bw/d

and the

oral LOAEL of 6 mg/kg bw/d

is judged to be sufficient even taking into account the use of a LOAEL.

Thus, the substance is of no concern with regard to repeated dose effects in relation to regional exposure via the environment.

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

Mutagenicity

4-tert-Butylbenzoic acid did not induce gene mutations in Salmonella. An in vitro micronucleus test with 4-tert-Butylbenzoic acid was weakly positive with metabolic activation. An in vivo test on chromosomal aberrations in rats was negative for doses which correspond to the MTD. There is sufficient evidence to conclude, that a clastogenic potential of ptBBA observed in vitro is unlikely to be expressed in germ cells in vivo.

However, due to the positive *in vitro* micronucleus test and the fact that clastogenicity and aneugenicity were not distinguished in this test there is concern for local clastogenic effects and aneugenic effects cannot be excluded. Therefore further testing for clarification is recommended, preferably a combination of an *in vivo* COMET assay (directly exposed tissue and liver) and a bone marrow micronucleus test.

The need for further testing to evaluate genotoxicity should be revisited in the light of limiting measure.

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Conclusion (i) On hold for further testing on genotoxic effects in vivo.

Carcinogenicity

The carcinogenic potential of 4-tert-butylbenzoic acid has not been examined. Thus, at present no conclusion can be drawn on the carcinogenic potential. However, positive results of further in vivo mutagenicity testing should be taken into considerations.for test strategies on carcinogenicity.

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

Reproductive toxicity

Fertility

MOS for the regional exposure scenario

The regional exposure has been estimated to $5.8 \cdot 10^{-6}$ mg/kg bw/d. The margin of safety between the

exposure level of $5.8 \cdot 10^{-6}$ mg/kg bw/d

and the

oral NOAEL of 1.6 mg/kg bw/d

is judged to be sufficient.

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

Developmental toxicity

Any hazard assessment for PTBBA with respect to developmental toxicity is not possible since there are no human or experimental data available. However, the decision of the C&L meeting in September 2007 with repr. Cat. 2, R60 has the consequences that restricting approaches of the substance will be initiated. Therefore, the need for a test to evaluate developmental toxicity should be revisited in the light of the risk reduction strategy.

Conclusion (i) On hold for further testing waiting for the outcome of risk reduction strategy if further possible measures are needed..

4.1.3.4.3 Summary of risk characterisation for exposure via the environment

The risk characterisation for indirect exposure of humans to PTBBA via the environment near point sources (local exposure level) as well as to regional exposure results in no concern with respect to repeat dose toxicity , carcinogenicity and male fertility (conclusion ii).

The C&L meeting in September 2007 decided for the substance repr. Cat2, R60. It is expected that the initated risk reduction measures will also protect for mutagenic as well for developmental toxic effects. Therefore, further testing is on hold for both toxicological endpoints in the light of the risk reduction strategy (conclusion i).

4.1.3.5 Combined exposure

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

4.2.1.1 Workers

See chapter 4.1.1.1.

4.2.1.2 Consumers

4.2.1.3 Humans exposed via the environment

4.2.2 Effects assessment: Hazard identification

4.2.2.1 Explosivity

PTBBA is not explosive.

4.2.2.2 Flammability

PTBBA is not flammable.

4.2.2.3 Oxidizing potential

Due to ist chemical structure, PTBBA is not expected to possess any oxidizing properties.

4.2.3 Risk characterisation

4.2.3.1 Workers

Not applicable

4.2.3.2 Consumers

4.2.3.3 Humans exposed via the environment

5 RESULTS [10]

5.1 INTRODUCTION

5.2 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 for the intermediate processing site and use as resin modifier due to negligible emissions. The conclusion covers also the life-cycle stages of the use as stabiliser in PVC (manufacture of liquid mixed metal stabilisers, compounding and conversion, service life and disposal) due to zero or low exposure. All the scenarios mentioned do not cause risks for the compartments water, sediment, waste water treatment plants, air and soil. In addition, conclusion (ii) applies to the marine environment due to low exposure and as the substance does not meet the PBT-criteria.

Bioaccumulation in the aquatic and terrestrial food chain is expected to be negligible. Consequently, no assessment of secondary poisoning was conducted.

5.3 HUMAN HEALTH

5.3.1 Human health (toxicity)

5.3.1.1 Workers

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

Conclusion (i) applies to mutagenicity. For adequate assessment of the genotoxic potential of 4-tert-butylbenzoic acid preferably a combination of an *in vivo* COMET assay (directly exposed tissue and liver) and a bone marrow micronucleus test is recommended.

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

Conclusion (i on hold) applies to developmental toxicity. Risk assessment with respect to developmental toxicity is not possible since there are no human or experimental data available. Conclusion (i on hold) is expressed keeping in mind that due to the low critical exposure level for systemic effects after repeated exposure (≈ 0.07 mg/m^3) risk reduction measures will be implemented, which could also cover risks regarding developmental toxicity.

[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.

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

Two occupational exposure scenarios have been identified: (1) production and further processing of PTBBA (2) Production of alkyd resins in the polymers industry.

For PTBBA, concern is expressed for systemic toxicity after acute and repeated contact and fertility effects, where systemic toxicity after repeated contact is the most relevant toxicological endpoint.

With respect to effects in the airways after repeated exposure, inhalation exposure levels of 4-tert-butylbenzoic acid should be controlled to values in the range of 0.067 mg/m^3 (critical exposure level of systemic effects after repeated exposure). In doing so, inhalation risks from other endpoints, especially risks of adverse fertility effects, as well as possible risks by developmental toxicity are similarly and effectively be mitigated too.

Special attention should be given to skin contact. From the risk assessment there is indication that repeated dermal exposure at the workplace to 4-tert-butylbenzoic acid may not exceed a daily exposure of 0.017 mg/kg/day or 1.2 mg/person/day. In doing so, dermal risks from other endpoints especially risks of adverse fertility effects and possible risks of developmental toxicity, as well as risks by acute toxicity are similarly and effectively be mitigated too.

5.3.1.2 Consumers

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

Conclusion(i on hold) applies to mutagenicity and developmental toxicity. The C&L meeting in September 2007 decided for the substance repr. Cat2, R60. It is expected that the initiated risk reduction measures will also protect consumers for mutagenic as well for developmental toxic effects. Therefore, further testing is on hold for both toxicological endpoints in the light of the risk reduction strategy (conclusion i).

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 other toxicological endpoints except mutagenicity and developmental toxcicity

5.3.1.3 Humans exposed via the environment

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

Conclusion (i on hold) applies to mutagenicity and developmental toxicity. The C&L meeting in September 2007 decided for the substance repr. Cat2, R60. It is expected that the initiated risk reduction measures will also protect for mutagenic as well for developmental toxic effects. Therefore, further testing is on hold for both toxicological endpoints in the light of the risk reduction strategy (conclusion i).

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 repeated dose toxicity carcinogenicity and male fertility.

5.3.1.4 Combined exposure

5.3.2 Human health (risks from physico-chemical properties)

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.

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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*, *bw*
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

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
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
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)

Appendix A

Confidential.

European Commission

EUR [ECB: click here to insert EUR No.] - European Union Risk Assessment Report [ECB: click here to insert SUBSTANCE NAME, and volume no.]

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The report provides the comprehensive risk assessment of the substance 4-tert.-Butylbenzoic acid It has been prepared by Germany 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. The environmental risk assessment concludes that there is no concern for any of the environmental compartments.

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 human health risk assessment concludes that there is concern for workers with regard to acute and repeated dose toxicity and fertility via inhalation and dermal contact during certain production scenarios. There is a need for further information and for testing for mutagenicity and for developmental toxicity (on hold). For all other endpoints for workers, consumers and for humans exposed via the environment and for human health (physico-chemical properties) there is no concern.