4-TERT-BUTYLBENZOIC ACID

CAS No: 98-73-7

EINECS No: 202-696-3

SUMMARY RISK ASSESSMENT REPORT

Final report, 2009

Germany

FINAL APPROVED VERSION

Rapporteur for the risk assessment of **4-tert-Butylbenzoic acid, (PTBBA)** is the Federal Institute for Occupational Safety and Health.

Contact point:

Bundesanstalt für Arbeitsschutz und Arbeitsmedizin
Anmeldestelle Chemikaliengesetz (BAuA)
(Federal Institute for Occupational Safety and Health
Notification Unit)
Friedrich-Henkel-Weg 1-25
44149 Dortmund (Germany)
fax: +49(231)9071-679
e-mail: chemg@baua.bund.de

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

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance **4-tert-Butylbenzoic acid, (PTBBA)** that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

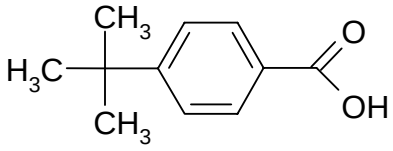
CONTENTS

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
Synonyms:	para-tert.-Butylbenzoic acid
	PTBBA
	4-(1,1-Dimethylethyl)benzoic acid
CA-Index name:	Benzoic acid, 4-(1,1-dimethylethyl)-
Molecular weight:	178.23 g/mol
Molecular formula:	$C_{11}H_{14}O_2$



Structural formula:

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

Table 1.1 Summary of physico-chemical properties

Property	Value	
Physical state	White crystalline powder	
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); [4)]	Clariant France, 2003
Partition coefficient n-octanol/water (log value)	LogPow 3.4 at 21 °C [5)]	Hoechst, 1993
Flash point	not conducted (solid)	
Ignition temperature	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

[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)] 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.

[4)] 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.

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

1.4 CLASSIFICATION

(Proposal of the rapporteur)

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 "R 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 level 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.

2 GENERAL INFORMATION ON EXPOSURE

Production

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

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.

Uses

According to industry information, PTBBA is mainly used in the EU for the manufacture of thermal stabilisers in PVC. For this purpose, PTBBA is first converted into its metal salts (Metal-p-tert-butylbenzoate, Me-PTBB). According to ESPA (European Stabiliser Producers Association) six plants are using PTBBA for the production of liquid mixed metal stabilisers. 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 indicates that liquid metal stabilisers are used in both major compounding methods and their subsequent conversion methods. Dry blending followed by calendering is the major use of these stabilisers.

The second most important use of PTBBA in the EU is the use as process regulator (chain stop agent) in polymers industry for producing alkyd and polyester resins. PTBBA is added into the polymerisation step of resin production where it reacts covalently with the usual alkyd monomers. 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.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Environmental releases

Since production has ceased in EU, PTBBA is expected to be released into the environment mainly during the production of liquid mixed metal stabilisers and their compounding and conversion as stabilizer in PVC. PTBBA is present from the conversion step to the metal stabiliser onward in its ionic form p-tert-butylbenzoate, 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.

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.

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.

Environmental fate

PTBBA is dissociated (ionised) in the environmentally relevant pH range. Water solubility and $\log K_{ow}$ are very much dependent on pH.

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.

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 1984 1 /id}. 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 1984 1 /id} and in some of the other tests indicate that PTBBA might be inherently biodegradable. 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.

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.

In the environmentally relevant pH range it is expected that PTBBA has a low potential to bioaccumulate. Therefore, the assessment of secondary poisoning is not conducted.

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

Environmental concentrations

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.

For the receiving environment, exposure at pH 5 and pH 7 are calculated. A pH of 7 is assumed according to the TGD for STPs in this assessment.

PECs - aquatic compartment (incl. sediment)

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 3.1.

Table 3.1 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	$PEC_{local\ stp}$ ($\mu g\ l^{-1}$)	$C_{local\ water}$ ($\mu g\ l^{-1}$)		$PEC_{local\ water}$ ($\mu g\ l^{-1}$)		$PEC_{local\ sediment}$ ($\mu g\ kg^{-1}$ 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	

PECs - Terrestrial compartment

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. 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$_{soil}$ (µg kg^{-1} wwt)		**PEClocal$_{groundwater}$ (µg l^{-1})**	
pH 7	pH 5	pH 7	pH 5
0.015	0.065	0.067	0.041

PEC - Atmosphere

Only for the use as stabiliser at PVC compounding and conversion sites emissions to air have been identified. 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.

Secondary poisoning

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

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

For the calculation of background concentrations, a market volume of 3,000 tpa has been used. The calculation uses the default characteristics of the TGD for the standard regional and continental environments. Table 3.2 presents the resulting regional and continental concentrations.

Table 3.2 $PEC_{regional}$ 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

Aquatic compartment (incl. sediment)

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, 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}

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}

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

Terrestrial compartment

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

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

Atmosphere

No data on adverse effects via atmosphere are available.

3.3 RRISK CHARACTERISATION

3.3.1 Aquatic Compartment

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 3.3.

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 3.3 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[2]	-	(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)
Region	0.03 0.004	(ii)		

- = negligible emissions to aquatic environment

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 are expected to be zero. Therefore, no risk characterisation ratios were calculated and conclusion (ii) applies.

Conclusion (ii) also applies to the regional scenario.

[2] Intermediate processing ceased in March 2007.

3.3.2 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.

3.3.3 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 3.4 Risk characterisation ratios for the terrestrial compartment.

Scenario	Soil	
	RCR (pH 5) RCR (pH 7)	Conclusion
Intermediate processing[3]	See $RCR_{regional}$ (Table 3.3)	(ii)
Use as stabilizer in PVC - production of PTBBA metal salts, all sites	See $RCR_{regional}$ (Table 3.3)	(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)

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. Therefore, no risk characterisation ratios were calculated and conclusion (ii) applies.

Conclusion (ii) also applies to the regional scenario.

[3] Intermediate processing ceased in March 2007.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

Based on the available information, 43 % of the PTBBA are used in the manufacturing of alkyd resins. 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.

Detailed information on the production volumes and the use of PTBBA is given in chapter 2.

Relevant occupational exposure scenarios are to be expected in the following areas:

- Further processing of PTBBA
- Production of alkyd resins in the polymer industry

Due to the low concentration of PTBBA (< 0.1 %) in resins it is assumed that the downstream uses of resins are not relevant for this assessment.

Occupational exposure limits (OEL) have not been established.

The exposure assessment is based on measured data and estimations according to the EASE model (Estimation and Assessment of Substance Exposure). The exposure levels should be regarded as reasonable worst case estimates representing the highly exposed workers.

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 Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m^3]	Dermal exposure Shift average [mg/p/day]

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m^3]	Dermal exposure Shift average [mg/p/day]
1a. Production of PTBBA salts	1 hour, daily	0.05 (workplace measurement)	42 (EASE, with gloves)
1b. PTBBA used as a chemical intermediate	shift length, daily	1 (EASE, low dust, with LEV)	42 (EASE, with gloves)
2. Production of alkyd resins in the polymer industry	30 min, daily	0.0625 (EASE, low dust, no LEV)	42 [2)] (EASE, with gloves)

Consumer exposure

There is no information for the use of consumer products containing 4-tert-butylbenzoic acid. The BfR-product database and other available European databases do not give evidence for use of 4-tert-butylbenzoioc acid in consumer products.

According to published data exposure may occur by contact with sex toys. Data to the content of 4-tert-butylbenzoic acid 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.

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.

The estimated daily human intake from indirect exposure on a local and regional scale is presented in Table 4.2.

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

4.1.2 Effects assessment

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 4-tert-butylbenzoic acid (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).

Acute toxicity

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. 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 ovaries of surviving female rats were of normal appearance and presented no histological evidence of abnormal oogenesis. The oral LD50 for mice was determined at 568 mg/kg bw. 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. The assessment of acute dermal toxicity is difficult, because the available data demonstrated great species differences. 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 20/21/22, Harmful by inhalation, in contact with skin and if swallowed".

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 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.

Corrosivity

4-tert-Butylbenzoic acid has proven to cause no skin irritation in rabbits and mild eye irritation in rabbits was reversible. Thus, PTBBA has no corrosive properties.

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.

Repeated dose toxicity

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 4-tert-butylbenzoic acid were the central nervous system, liver, kidneys, testes, epididymides, hemopoietic system and the thymus. Regional poliomyelomalacia and responsive gliosis of the spinal cord can be associated to the fore and hind limb paralysis and gait abnormalities that were 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 a oral study. 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, a LOAEL of 100 ppm (6 mg/kg bw/d) for the oral route from the 90-day study and a LOAEL of 7.5 mg/kg bw/d for the dermal route from the 28-day study.

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 4-tert-butylbenzoic acid 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 4-tert-butylbenzoic acid 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 September 2007 the TC C&L agreed T; R48/23/24/25.

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 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 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 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.

Carcinogenicity

At present, the carcinogenic potential of 4-tert-butylbenzoic acid 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.

Toxicity for reproduction

Any hazard assessment for 4-tert-butylbenzoic acid 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 4-tert-butlybenzoic acid 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 4-tert-butlylbenzoic acid 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 4-tert-butylbenzoic acid 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 the following table

Route of application	NOAEL/C	LOAEL/C
Oral	1.6 mg/kg bw/d	7.9 mg/kg bw/d
Oral/ 90 days	-	6 mg/kg bw/d
Dermal/ 7 and 13 weeks	35 mg/kg bw/d	70 mg/kg bw/d
Dermal / 28 days	30 mg/kg bw/d	60 mg/kg bw/d
Inhalation/ 4 days (3 days rest) 3 days	-	12.5 mg/m^3

Since a clear-cut toxic potential specifically adverse to male gonads and resulting in impaired male fertility in rats was revealed for 4-tert-butylbenzoic acid 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

Workers

Introduction to occupational risk assessment

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). The threshold levels identified in the hazard assessment are taken forward to this occupational risk assessment.

According to the data on toxicokinetics, metabolism and distribution the absorption is estimated to be 100% (default values) for oral, dermal and inhalation exposure.

In the following table the exposure levels of table 4.1 are summarised and the route-specific and total internal body burdens are identified.

Table 4.2: 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/day		
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

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 a conversion of 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 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 m^3) and the respiratory volume for light activity (10 m^3).

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 are 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 as interspecies and intraspecies differences, differences in duration, uncertainty in route-to-route extrapolation and dose-response relationship including severity of effect. In the case that no detailed data are available for these assessment factors, default values are recommended.

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.

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/m^3 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”.

Acute Toxicity

Local effects ***see irritation, no further information available***

systemic effects

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 litre over 4 hours resulted in death in 2/6 male and 1/6 female rats.

Inhalation exposure

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

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.

The reference MOS consists of (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. This gives a reference MOS of 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. Peak exposure levels are not available.

Dermal contact and combined exposure

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

For assessing the acute dermal and combined toxicity of PTBBA a subacute 28 day rat study is taken (for more details see chapter 4.1.2 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 and combined toxicity and serves as well as internal and as external starting point, because the absorption percentage for the oral and dermal pathway is 100%.

For 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. Altogether the reference MOS calculates to 50 (4 • 2.5 • 5) the corresponding external and internal 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 exposure scenarios for dermal and combined exposure.

Irritation/Corrosivity

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

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.

Respiratory tract

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

Sensitisation

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

Skin sensitisation

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.

Respiratory sensitisation

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.

Repeated dose toxicity

Local effects (RDT) by inhalation or dermal contact

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

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.

Systemic effects (RDT)

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

Inhalation exposure

In several subacute inhalation studies liver weight changes are the most sensitive parameter (at concentrations of 15 mg/m^3), a reduction of testes weight occurs at 106 mg/m^3. The 28-day inhalation study serves as key study to assess systemic risks by inhalation. 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 gives an adjusted inhalation starting point of 2.5 mg/m^3 (5 • 6/8 • 6.7/10).

The reference MOS consists of (1) an interspecies factor of 2.5 (the factor for allometric scaling is already implicitly applied), (2) an intraspecies factor (workers) of 5 and (3) a reduced duration adjustment factor of 3 because, N(L)OAELs from studies with variable duration show only little differences (for detailed explanation see comprehensive RAR in the chapter MOS Approach). This gives a reference MOS of 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.

Dermal contact and combined exposure

For assessing toxicity after dermal contact a 28-day rat study is taken. Starting point after repeated exposure is the LOAEL of 7.5 mg/kg/day based on the liver weight increases of female rats.

The reference MOS consists of: (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 comprehensive RAR under chapter "MOS Approach"). Altogether 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.

Because of the concern for both exposure routes, for combined exposure automatically concern is reached. No specific calculation for PTBBA is done for combined exposure after repeated contact.

Mutagenicity

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

PTBBA 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.

Carcinogenicity

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

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 concern for workers with regard to carcinogenicity of 4-tert-butylbenzoic acid is not expressed.

Reproductive toxicity, developmental effects

Fertility impairment

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

PTBBA shows a toxic potential to male fertility in several studies with rats after inhalation, dermal or oral route of exposure. Also a study on occupationally exposed workers with PTBBA shows a slightly higher number of individuals with low sperm count.

For occupational risk assessment of fertility impairment an oral one-generation rat study is taken. 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. 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 inhalation 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 gives an inhalation starting point of 2.8 mg/m^3 (1.6 • 1/0.38 • 6.7/10).

The reference MOS consists of (1) the interspecies factor of 2.5 for remaining differences and (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.

Dermal and combined exposure

The NOAEL of 1.6 mg/kg/day resulting from the one-generation rat study is taken. The starting point for dermal and combined exposure is 1.6 mg/kg/day because for dermal absorption 100% in assumed. This value is divided by the reference MOS of 50 (a factor of 4 x 2.5 (rat) for interspecies and a factor of 5 for intraspecies differences). The corresponding critical internal and external exposure level calculates to 0.03 mg/kg/day (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.

Developmental effects

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

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. 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.

Summary of occupational risk assessment

The toxicological profile of 4-tert-butylbenzoic acid is characterised by the toxicological effects at the liver, kidneys, the central nervous system and male reproductive organs. 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.

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 4.3 (inhalation) and 4.4 (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 4.3: 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/m³		
		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 4.4: Ranking of health risks for workers (dermal contact)

Exposure scenario	Exposure level in mg/kg/day	Repeated dose toxicity, systemic	Fertility impairment	Acute toxicity systemic
		Critical exposure level in mg/kg/day		
		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

Consumers

There is no information for the use of consumer products containing 4-tert-butylbenzoic acid 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. 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 4-tert-butylbenzoic acid 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)**

Irritation / corrosivity

In Draize tests with rabbits the substance did not cause any signs of irritation to the skin of rabbits. **Conclusion (ii)**

Sensitisation

4-tert-butylbenzoic acid did not produce dermal sensitization in guinea pigs in a maximization test. **Conclusion (ii)**

Repeated dose toxicity

Dermal exposure
In a 28-day dermal study groups of male and female rats received 7.5, 15, 30 and 60 mg/kg bw/d 4-tert-butylbenzoic acid 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 aqueous solutions (1 ml/kg bw) containing the diethanolamine salt of 4-tert-butylbenzoic acid 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 4-tert-benzoic acid. 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 4-tert-butylbenzoic acid. A the testicular effects were marked, no effects were detected in males exposed to the lower doses.

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)**

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 4-tert-butylbenzoic acid 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 considerations. **Conclusion (ii)**

Toxicity for reproduction

Fertility

Several studies with rats via different routes of application (oral diet, inhalation, dermal) revealed the potential of 4-tert-butylbenzoic acid 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.

Concern on possible spermatotoxic effects of 4-tert-butylbenzoic acid 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.

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)**

Developmental toxicity

Any hazard assessment for 4-tert-butylbenzoic acid 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 for limiting the substance in consumer products by effective C&L protection measures on reprotoxicity.

Humans exposed via the environment

According to the calculations an intake of 4-tert-butylbenzoic acid via air is negligible.

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. 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 4-tert-butylbenzoic acid (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. 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.

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)**

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 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 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 limiting measures. **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)**

Reproductive toxicity

Fertility

Several studies with rats via different routes of application (oral diet, inhalation, dermal) revealed the potential of 4-tert-butylbenzoic acid 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. Concern on possible spermatotoxic effects of 4-tert-butylbenzoic acid 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:

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 limiting approaches are needed.**Conclusion (ii)**

Developmental toxicity

Any hazard assessment for 4-tert-butylbenzoic acid 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 in the light of limiting measures.

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)**

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 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 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. **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)**

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)**

Developmental toxicity

Any hazard assessment for 4-tert-butylbenzoic acid 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 revisited in the light of limiting measures.

Conclusion (i) On hold for further testing in the light of limiting measures.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

5 RESULTS

5.1 ENVIRONMENT

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

Conclusion (ii) applies to the 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. The risks have been assessed for environments at pH 7 and at pH 5, respectively. 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.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

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

This conclusion 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.

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 endpoints acute toxicity (inhalation), irritation, sensitisation and carcinogenicity.

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

Conclusion iii applies to dermal acute toxicity, repeated dose toxicity, and fertility effects.

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, systemic toxicity after repeated contact is the most relevant toxicological endpoint. For inhalation exposure the critical exposure level of ~0.07 mg/m^3 is derived, for dermal exposure a critical exposure level of ~0.02 mg/kg/d serves as trigger for concern.

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

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 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).

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.

5.2.2 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.