Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of
p-tert-butylphenol

EC number: 202-679-0
CAS number: 98-54-4

ECHA/RAC/CLH-O-0000002629-66-01/A1

Adopted

12 June 2012

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TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: p-tert-butylphenol

EC Number: 202-679-0

CAS number: 98-54-4

Registration number (s):

Purity: >= 96% w/w (SASOL, Germany, GmbH)

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

p-tert-butylphenol was on the 4th priority list of the Existing Substances Regulation and its classification was reviewed in the context of the Risk Assessment Procedure as it was a requirement to harmonise classification for all endpoints.

The classification of p-tert-butylphenol was discussed at ECB by the TC C&L in September 2005, March 2006 and September 2007.

In September 2005 TC C&L agreed to N; R 51/53 (Annex III).

In March 2006 TC C&L agreed to Xi; R 37/38 - R 41 (Annex II). In September 2007 TC C&L agreed to Repr. Cat.3; R62 (Annex I).

Proposed classification based on Directive 67/548/EEC criteria:

Xi; R37/38, R41

Repr. Cat 3; R62

Proposed classification based on CLP criteria:

STOT SE 3; H335

Skin Irrit. 2; H315

Eye Dam. 1; H318

Repr. 2; H361f

Proposed labelling based on Directive 67/548/EEC criteria:

Class of danger: Harmful (Xn)

R phrases: 37/38-41-62

S phrases: (2-)26-36/37-39-46

Proposed labelling based on CLP criteria:

Pictograms: GHS05, GHS07, GHS08

Signal Word: Danger

Hazard Statement codes: H361f, H335, H315, H318

Precautionary statements: Not required as PS are not included in Annex VI

Proposed specific concentration limits (if any): none

Proposed notes (if any): none

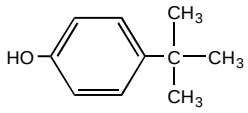
JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	p-tert-butylphenol
EC Name:	4-tert-butylphenol
CAS Number:	98-54-4
IUPAC Name:	4-(1,1-Dimethylethyl)phenol

1.2 Composition of the substance

Chemical Name:	p-tert-butylphenol
EC Number:	202-679-0
CAS Number:	98-54-4
IUPAC Name:	4-tert-butylphenol
Molecular Formula:	$C_{10}H_{14}0$
Structural Formula:	
Molecular Weight:	150.22
Typical concentration (% w/w):	>= 96% w/w (SASOL, Germany, GmbH), <= 4% w/w impurities unknown
Concentration range (% w/w):	

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties

REACH ref Annex, §	**Property**	**IUCLID section**	**Value**	**Reference**
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	White flakes at 20 °C	
VII, 7.2	Melting/freezing point	3.2	Ca 100 °C	Huels AG, Marl (A), 1992
VII, 7.3	Boiling point	3.3	237.5 °C at 1,013 hPa,	Huels AG Marl (A), 1992
VII, 7.4	Relative density	3.4 density	0.92 g/cm^3 at 110 °C, however at this high temperature, ptBP is in the liquid state.	Huels AG Marl (A), 1992
VII, 7.5	Vapour pressure	3.6	0.5 Pa at 20 °C, 1.3 x10^2 Pa at 60 °C	Huels AG Marl (B), 1994 SIDS
VII, 7.6	Surface tension	3.10		
VII, 7.7	Water solubility	3.8	**conc. at sat. (g/l)** 0.5 (at 25 °C) 0.61 (at 25 °C) 0.8 (at 25 °C)	 (Huels AG Marl (A), 1992) (SIDS, SIAP, 2000) (Boddeker *et al*., 1990)
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	**Experimental :** 2.44 and 3.31 3.29 at 25 °C **Calculated:** 3.42 QSAR	 Method: Flask shaking, Huels AG Marl (C) and (D), 1972 Method: OECD 107, SIDS, SIAP Epiwinsuite v3.1
VII, 7.9	Flash point	3.11	**open cup:** About 115 °C	Huels AG Marl (C)
VII, 7.10	Flammability	3.13	Flammability upon ignition (solids): no data available	

			Flammability-on contact with water: The classification procedure needs not to be applied because the organic substance does not contain metals or metalloids. Pyrophoric properties of solids: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).	

VII, 7.11	Explosive properties	3.14	The classification procedure needs not to be applied because there are no chemical groups present in the molecule which are associated with explosive properties.	
VII, 7.12	Self-ignition temperature		The study does not need to be conducted for solids, because the substance has a melting point < 160°C.	
VII, 7.13	Oxidising properties	3.15	The classification procedure needs not to be applied because the organic substance contains oxygen, which is chemically bonded only to carbon.	
VII, 7.14	Granulometry	3.5		
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17		
XI, 7.16	Dissociation constant	3.21		
XI, 7.17,	Viscosity	3.22	2.4 mPa s at 100 °C	Huels AG Marl (A, 1992)
	Auto flammability	3.12	510 °C	Huels AG Marl (A), 1992
	Reactivity towards container material	3.18		
	Thermal stability	3.19		
	[enter other property or delete row]			

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

Industrial:

The major use is as a monomer in chemical synthesis, e.g. for the production of polycarbonates, phenolic resins, epoxyresins etc. The material is also hydrogenated to the corresponding cyclic alcohol. Very minor amounts are used for the production of oilfield chemicals and as an intermediate for the production of an active ingredient in agrochemicals.

General public:

Consumer exposure is possible via direct use of products with phenolic resins- or epoxy resins containing residual p-tert-butylphenol (ptBP), or via use of the final articles containing residual concentrations of ptBP.

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

No classification.

3.2 Self classification(s)

4 ENVIRONMENTAL FATE PROPERTIES

Environmental classification of p-tert-butylphenol was discussed and in September 2005 the environment working Group agreed on the classification N; R 51/53. However as the criteria for environmental classification are changed in CLP, the criteria are no longer fulfilled and environmental classification is therefore not presented in this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Table 2: Acute toxicity, oral

Species	LD50(mg/kg)	Observations and Remarks	Ref.
Sprague-Dawley rats male/ female	> 2000	Performed according to OECD Test Guideline 401 GLP: yes. No deaths and no signs of systemic toxicity were noted during a 14 days observation period.	Sandoz Chemicals (1991)
Rats males/ femals	4000	Performed according to OECD Test Guideline 401.	Huels, 1985a
Sprague-Dawley rats, males	5360	No further data available..	Klonne *et al*., 1988
Sprague-Dawley rats, female	3620	No further data available.	Klonne *et al*., 1988
Wistar rats, male	2990	No further data available.	Smyth *et al*., 1969
Rats, males/ Females	3500	No further data available.	BASF, 1971
Wistar rats males/ Females	801	In this study ptBp was dissolved in 10 % DMSO, and the volume of the test solution increased with increasing dose of ptBP.	Shell, 1980
Guinea pigs, sex not specified		No LD50 was identified in this study, however, a LD0 was 400 mg/kg and a LD100 was 1400 mg/kg.	The Dow Chem. Co (referred in OECD-SIDS 2000)

5.2.2 Acute toxicity: inhalation

Table 3: Acute toxicity, inhalation

Species	LC50 (mg/l)	Exposure time (h/day)	Observations and Remarks	Ref.
Sprague-Dawley rats	> 5600 mg/m^3	4h hours,	In this limit test rats were exposed once for 4h in a 120 liter chamber.	Klonne *et al*., 1988
Sprague-Dawley rats		6 hours	In this study no lethality was reported when rats were exposed to an atmosphere saturated with ptBP for 6 hours. 100 g ptBP had been placed for 18 hours prior to the introduction of the animals.	Klonne *et al*., 1988 /UCC 1985
Rats		8 hours	In this study no lethality was reported when rats were exposed to an atmosphere saturated with ptBP for 8 hours.	BASF 1971

5.2.3 Acute toxicity: dermal

Table 4: Acute toxicity, dermal

Species	LD50 (mg/kg)	Observations and Remarks	Ref.
New Zealand Rabbits	>16. 000	In this study ptBP remained in contact with the skin for 24 hours under occlusive conditions. No lethality was observed in this study.	Klonne *et al*., 1988/ UCC 1985
New Zealand Rabbits	2318	In this study ptBP was applied to clipped trunk and retained for 24 hours beneath an impervious plastic film. The study was said to follow a modified Draize method. No further information is given.	Smyth , 1969

5.2.4 Acute toxicity: other routes

No data available.

5.2.5 Summary and discussion of acute toxicity

PtBP appears to have low acute toxicity by all three exposure routes. A limit test gives a LC_{50} for inhalation above 5600 mg/m^3 (dust aerosol) with no lethality observed. Signs of mucosal and respiratory alterations were observed and they are described in section 5.3.3. Most studies show dermal and oral LD_{50} values above 2000 mg/kg bw. The exception is an oral rat study

(Shell, 1980) where a LD_{50} of 801 mg/kg bw was derived. In this study the increasing volumes of DMSO used for intubation of increasing doses of ptBP may be an explanation of the elevated acute toxicity observed in this study compared to the other acute oral toxicity studies reported.

Conclusion:

No classification for acute toxicity for oral, inhalation and dermal exposure according to CLP criteria is proposed.

5.3 Irritation

5.3.1 Skin irritation

Table 5: Irritation, skin

Species	No. of	Exposure time (h/day)	Conc.	Dressing: occlusive semi-occlusive open	Observations and remarks	Ref.
New Zealand Rabbits	1 male 2 females	4 hours	500 mg moisted with distilled water	Semi-occluded	This study was performed according to OECD Test Guideline 404, and under GLP conditions. Skin reactions were scored according to Draize at one hour, 24, 48 and 72 hours, and 7 and 14 days after dosing. The material produced severe erythema and very slight to moderate oedema. The mean scores for erythema were as follows: 24 hours, score 4; 48 hours, score 4; 72 hours, score 3.3; 14 days, score 0. Average score for erythema over 24-48-72 hours was 3.8. Mean scores for oedema were: 24 hours, score 2; 48 hours, score 1.3; 72 hours, score 1.7; 14 days, score 0. Average score for oedema over 24-48-72 hours was 1.7. Other adverse skin reactions noted were small areas of white-coloured necrosis (all exposed skin sites at 24 and 48 hours), well-defined erythema surrounding scabs, hardened light brown-coloured scab, thickening of the skin, crust formation and reduced re-growth of fur. No	Sandoz Chemicals, 1991

					irreversible skin alterations were reported after 14d and the substance was judged to be non-corrosive according to EU classification criteria (full thickness destruction of the skin). The lesions reported indicate that ptBP is highly irritating to skin.	
New Zealand rabbits	3 males 3 females	4 hours	500 mg moisted with water	Semi-occluded	In this study skin reactions were scored according to Draize at one hour, 24, 48 and 72 hours, and 7, 10, 14 and 17 days after dosing. No signs of dermal irritation were observed in 4 of 6 rabbits. One female rabbit developed transient erythema (grade 1; day 1) and persisting desquamation (day 10-17), and one male rabbit showed erythema (grade 1-2; day 1-10), minor oedema (grade 1; day 1-3), desquamation (day 10-14), scab formation (day 7-10) and necrosis (day 1-10). This study indicates that ptBP can be severely irritating and possible also corrosive to skin.	Klonne *et al*., 1988/ UCC 1985
New Zealand Rabbits	3 males 3 females	4 hours	500 mg	(semi-)occluded skin	This study was performed according to OECD Guideline 404, and skin reactions were scored according to Draize at one hour, 24, 48 and 72 hours, and 6, 8, 10, and 14 days after dosing. Erythema was well defined in 2 of 6 animals and moderate to severe in 4 of 6 animals. Oedema was very slight in 4 of 6 animals, and moderate in 2 of 6 animals at 24 hours. Erythema and oedema was present in some animals through day 10. Scabs and desquamation persisted in 3 of 6 animals at day 14. This study indicates that ptBP is irritating to skin.	Huels, 1985b
New Zealand Rabbits	5 males 1 female	4 hours	500 mg moisted with saline	Semi-occluded	In this study the skin irritation of ptBP was studied according to US DOT regulation 173.1300. Skin reactions were observed after removal of the patch and approximately 48	Schenectady, 1982

					hours thereafter. Mean scores: Erythema: 4 hours, score 2; 48 hours, score 2.3. Oedema: 4 hours, score 1.5; 48 hours, score 1.7. One male showed necrosis at 48 hours. No further details are provided. The primary irritation index was found to be 3.4 on a scale to 8. This study supports the indications that ptBP can be severely irritating and also corrosive to skin.	
Rabbits	3 males 3 female	4 hours	500 mg	Intact or abraded skin in an occlusive patch test	In this study skin reactions were scored according to Draize at 24, 48 and 72 hours, and at 7 days after dosing. The following mean scores for non-abraded skin was reported: Erythema: 24h: 1.7; 48h: 1.1; 72h: 0.2; 7d: 0.6. Oedema: 24h: 0.8; 48h: 0.7; 72h: 0.4; 7d: 0.2. For abraded skin, the mean scores were:Erythema: 24h: 1.8; 48h: 1.7; 72h: 1.3; 7d: 1.0. Oedema: 24h: 0.8; 48h: 0.8; 72h: 0.6; 7d: 0.3.Three of the animals were reported to have small white areas of skin similar in appearance to a burn. No details of reversibility of these effects were reported. In this study ptBP was regarded as mildly irritating to rabbit skin.	Shell, 1980
New Zealand Rabbits	5 males 5 female	24 hours	2000, 8000, 16 000 mg/kg bw	Occlusive	This study was a percutaneous acute toxicity study and dermal application of 2000, 8000 and 16000 mg/kg bw ptBP for 24 hours produced severe irritation and dermal necrosis. Severe skin irritation (including erythema, oedema, fissuring, desquamation and necrosis) were noted in both sexes of all treatment groups. For the middle and high dose groups necrosis generally persisted through the 14-days post-exposure period. For the low dose animals (2000 mg/kg bw) signs of erythema, necrosis and fissuring were present through day 7,	Klonne *et al*., 1988/ UCC 1985

					whereas desquamation and scabs were present at day 14.	
Black Guinea pigs	5 males 5 female	24 hours Every weekday for 3 weeks	0.1 ml solutions of ptBP in various liquid solvents (DMSO, acetone, and propylene glycol).	PtBp was applied to shaved skin	In this depigmentation test irritation was induced. 1 mg and 5 mg of ptBP induced no irritation and mild irritation, respectively. 10 mg of ptBP in acetone induced strong skin irritation (erythema and oedema extending beyond area of application), whereas 10 mg of ptBP both in DMSO and in propylene glycol induced moderate irritation.	Gellin *et al*., 1970

5.3.2 Eye

Table 6: Irritation, eye

Species	**No. of animals**	**Exposure time (h/day)**	**Conc)**	**Observations and remarks (specify the experimental conditions, score and evaluation method)**	**Ref.**
Rabbits	6 animals	24 hours	80 mg of finely ground dry pounder	In this study ptBP produced severe corneal injury, iritis and severe conjunctival irritation. The scoring was conducted according to Draize. The following mean scores were reported: Corneal opacity of grade 1 (1 h) to 3.2 (7d), iris lesion grade 1, conjunctival redness of grade 1.8 (1h) to 2.2 (72h), and chemosis of grade 2.3 (1h) to 3.8 (72h). Due to corneal opacity, the scoring of iris lesions after 4h was not possible in many animals and thus reversibility could not be established. The corneal opacity was significant 21 days after exposure (mean score 2.5; range 0-4). Application of smaller amounts of the material (10 mg) resulted in similar but less severe effects, which persisted in most eyes for the 21-day observation period. This study shows that ptBP is highly irritating to rabbit eyes.	Klonne *et al*., 1988/ UCC 1985
New Zealand Rabbits	6 animals	24 hours	100 mg	Eye injury was scored at 1, 24, 48 and 72 hours, and 7 days post-exposure according to the method of Draize. The following mean scores were obtained: corneal opacity grade 0 (1h) to grade 1.4 (48h-7d), iris lesions grade 0 (1h) to 0.5 (48h-7d), conjunctival redness grade	Shell, 1980

				2 (1h-48h) to 1.2 (7d), chemosis grade 2.2 (24h) to 0.3 (7d). This study indicates that ptBP is irritating to rabbit eyes.	
				Severe irritation and probabaly corrosive effects were mentioned in another test. However, no detailed information was available for this study.	BASF, 1971

5.3.3 Summary and discussion of irritation

***Skin irritation*:**

Six studies in rabbits and one in Guinea pigs are available.

Table 7: Skin irritation studies (see details in table 5)

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

In the most recent study (Sandoz Chemicals, 1991), p-tert-butylphenol was found to be highly irritating to skin. In this guideline study (OECD TG 404), following GLP, 500 mg of p-tert-butylphenol was moistened with distilled water and applied (semi-occluded), to the intact skin of three New Zealand rabbits (1 male and 2 females), for 4 hours. Skin reactions (erythema, eschar formation, oedema) were scored according to Draize at one hour, 24, 48 and 72 hours, as well as 7 and 14 days after treatment. The mean scores for erythema were as follows: 24 hours, score 4; 48 hours, score 4; 72 hours, score 3.3; 14 days, score 0. Average score for erythema over 24-48-72 hours was 3.8. Mean scores for oedema were: 24 hours, score 2; 48 hours, score 1.3; 72 hours, score 1.7; 14 days, score 0. Average score for oedema over 24-48-72 hours was 1.7.

Other adverse skin reactions noted were: small areas of white-coloured necrosis and well-defined erythema surrounding scabs in all exposed animals at 24 and 48 hours and in two exposed animals at 72 hours; hardened light brown-coloured scabs and thickening of the skin at two treated skin sites at day 7, and reduced re-growth of fur at these sites at day 14; crust formation at one treated skin site at day 7. No irreversible skin alterations were reported after 14 days, and as no further information on the nature of the white coloured necrosis is provided, it is considered that p-tert-butylphenol is not corrosive according to classification criteria in CLP and DSD (full thickness destruction of the skin).

The lesions reported indicate that p-tert-butylphenol is severely irritating to skin.

In a skin irritation study by Klonne *et al* (1988), 4 hours of occluded application of 0.5 g p-tert-butylphenol produced no irritation in 4 out of 6 rabbits. Minor, transient erythema developed in one rabbit by day 1, with desquamation evident during days 10-17 post exposure. One of 6 rabbits exhibited slight oedema on days 1-3, dermal necrosis on days 1-10, scab formation on days 7-10, desquamation on days 10-14. The skin of this rabbit appeared normal on day 17 post exposure..

In a skin irritation study from Huels (1985b), 4 hours of (semi-)occluded application of 0.5 g p-tert-butylphenol produced signs of irritation in all 6 rabbits. The test substance was put in a patch test on the clipped back skin. The average score for erythema over 24-48-72 hours was 2.4, for oedema this was 1.6. Scab or scale formation was observed on days 6, 8, 10 and 14 post exposure (in 4, 4, 5 and 3 animals, respectively), and detaching of the skin on days 8, 10 and 14 post exposure (in 2 animals per time point).

In a skin irritation study conducted according to US DOT regulation 173.1300 (Schenectady, 1982), 500 mg p-tert-butylphenol moistened with saline was applied for 4 hours (semi-occluded) to the intact skin of New Zealand rabbits (1 female and 5 males). Skin reactions were observed after removal of the patch and approximately 48 hours thereafter. Mean scores for the effects seen were as follows: Erythema: 4 hours, score 2; 48 hours, score 2.3. Oedema: 4 hours, score 1.5; 48 hours, score 1.7. One male showed necrosis at 48 hours. No further details are provided.

Two studies with prolonged exposure during 24 hours are available.
In a percutaneous toxicity study with rabbits (Klonne *et al*,1988), signs of severe skin irritation were reported in all exposed animals after prolonged skin contact (24 hours) with doses of 2, 8 and 16 g/kg. The effects seen were erythema, oedema, fissuring, desquamation and/or necrosis in both sexes in all dose groups. For animals dosed with 8 and 16 mg/kg signs of skin irritation generally persisted at 14 days post exposure. For rabbits dosed with 2 mg/kg bw, signs of erythema, necrosis and fissuring was seen through day 7, and desquamation and scabs were still present at day 14. No information related to the nature of the corrosivity and necrosis reported is available.

In a skin irritation study (Shell, 1980) with occlusive patch testing according to the method of Draize, intact and abraded skin of rabbits were exposed for 24 hours to 500 mg of ptBP. Mean scores at each observation time (24, 48, 72 h, and 7 days) were registered for erythema, oedema only. The primary irritation score according to the method of Draize was 2.04 and in the study report it was concluded that ptBP was to be regarded as mildly irritating to rabbit skin based on the effects seen. It was also mentioned that three of the six animals in the study had small white areas of skin similar in appearance to a burn, and it is stated that this may be due to a protein denaturing effect of the compound.

Comparison with criteria:

Criteria for Skin Irrit. 2; H315	**Data fulfilling the criteria**
(1). Mean value of ≥ 2,3 - ≤ 4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from grading at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.	Sandoz Chemicals, (1991): Erythema: 24 hours, score 4; 72 hours, score 3.4; 14 days, score 0, with average score 3.8. No irreversible skin alterations were reported after 14 days and the substance was judged to be non-corrosive. Klonne et al (1988), Percutaneous toxicity study: 2, 8 and 16 g/kg bw p-tert-butylphenol for 24 hours produced severe irritation and dermal necrosis. Severe skin irritation (including erythema, oedema, fissuring, desquamation and necrosis) were noted in both sexes of all treatment groups. For the middle and high dose groups necrosis generally persisted through the 14-days post-exposure period. For the low dose animals (2 mg/kg bw) signs of erythema, necrosis and fissuring were present through day 7, whereas desquamation and scabs were present at day 14. Klonne et al (1988), Skin irritation study: 6 animals. One rabbit developed transient erythema (grade 1; day 1) and persisting desquamation (day 10-17), and one rabbit showed erythema (grade 1-2; day 1-10), minor oedema (grade 1; day 1-3), desquamation (day 10-14), scab formation (day 7-10) and necrosis (day 1-10). This study indicates that p-tert-butylphenol can be severely irritating and possible also corrosive to skin. Huels (1985): Erythema was well defined in 2 of 6 animals and moderate to severe in 4 of 6 animals, with an average score of 2.4. Oedema was very slight in 4 of 6 animals, and moderate in 2 of 6 animals at 24 hours. Erythema and oedema was present in some animals through day 10. Scab or scale formation and detaching of skin was observed in some animals from day 6 post exposure. Schenectady (1982): Erythema: 4 hours, score 2; 48 hours, score 2.3. Oedema: 4 hours, score 1.5; 48 hours, score 1.7. One male showed necrosis at 48 hours

Classification as skin corrosive (H314) is discarded because:

(i) Skin corrosion should be applied to substances where irreversible skin damage is seen after up to 4 hour exposure. PtBP did not induce any irreversible skin lesions or full skin destruction in a skin irritation study according to OECD test guidelines and GLP, with exposure for 4 h in semi-occluded intact skin in rabbits. There are reports of necrosis in several studies, but there are doubts concerning the interpretation of these effects as the skin was reported to look normal at the end of the observation period, and necrosis is per definition not reversible;

(ii) in the 1 of 6 animal with indication of necrosis in the study of Klonne *et al* (1988), normal skin was observed at day 17 post exposure; and

(iii) in the 1 animal of 6 in the study by Schenectady *et al* (1982) for which necrosis at 48 h was indicated, no details are reported.

On the basis of the effects seen and the arguments listed above, RAC agreed that ptBP should be classified as Skin Irritant, Category 2, according to the CLP Regulation.

Conclusion:
Based on the animal data available, classification according to CLP criteria with Skin Irrit. 2; H315 (Xi; R38 according to Directive 67/548/EEC) is proposed.

Note: Classification Xi: R38 (Skin Irrit. 2; H315 according to the CLP Regulation) was agreed at TC C&L in March 2006.

Eye irritation:

In three studies p-tert-butylphenol was shown to be highly irritating to rabbit eyes, and the severe irritating effects persisted during the 7- and 21-day observation period.

Comparison with criteria:

Criteria for Eye Dam. 1; H318	**Data fulfilling the criteria**
- at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or - at least in 2 of 3 tested animals, a positive response of: - corneal opacity ≥ 3 and/or - iritis > 1,5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.	(Klonne 1988). Corneal opacity of grade 1 (1 h) to 3.2 (7d), iris lesion grade 1, conjunctival redness of grade 1.8 (1h) to 2.2 (72h), and chemosis of grade 2.3 (1h) to 3.8 (72h). Due to corneal opacity, the scoring of iris lesions after 4h was not possible in many animals and thus reversibility could not be established. The corneal opacity was significant 21 days after exposure (mean score 2.5; range 0-4). (Shell 1980) corneal opacity grade 0 (1h) to grade 1.4 (48h-7d), iris lesions grade 0 (1h) to 0.5 (48h-7d), conjunctival redness grade 2 (1h-48h) to 1.2 (7d), chemosis grade 2.2 (24h) to 0.3 (7d). (Basf 1971). Severe irritation and probably corrosive effects were mentioned in another test.

Conclusion:

Based on the above information ptBP is regarded as severely irritating to eyes and classification according to CLP criteria with Eye Dam. 1 - H318 is proposed (Xi; R41 according to Directive 67/548/EEC).

Note: Classification with Xi: R41 (Eye Dam. 1 - H318 according to the CLP Regulation) was agreed at TC C&L in March 2006.

5.4 Corrosivity

5.5 Sensitisation

5.5.1 Skin

Table 8: Sensitisation, skin

Species	Type of test	No. of animals	Incidence of reactions observed	Ref.
Guinea pigs (Dunkin Hartley, young males)	Magnusson-Kligman	10 test animals 5 control animals	In this study ptBP was found not to be sensitising. The study was conducted according to OECD guideline 406 and according to GLP. In a preliminary study appropriate test substance concentrations were established by intracutaneous injection. The concentrations in the preliminary study were 0, 0.01, 0.05, 0.1, 0.5, 1.00, 5.00% of ptBP in corn oil. The two highest concentrations induced necrosis 24 hours after injection. For dermal occlusive application two patches on each flank were exposed to 5, 10, 25, 50% (w/w) ptBP i Vaseline. The 25 and 50% formulations caused discrete to intense erythema and swelling combined with necrosis and eschar formation after 48 and 72 hours. The exposure concentrations used for the induction phase were 0.5% in corn oil for intracutaneous induction and 10% in Vaseline for the topical induction, whereas 1% in Vaseline, the highest non-irritating concentration, was used for the challenge treatment. In the main study the skin reactions to the topical induction were evaluated 48 and 72 hours after application. The challenge treatment was carried out with 1% test compound in Vaseline. The treatment caused no skin reactions. The results demonstrated no evidence of skin sensitisation.	Huls, 1998
Guinea pigs (Dunkin Hartley, young females)	Modified Magnusson-Kligman	24 test animals 6 positive control animals, 12 negative control animals	In this study ptBP was found to be not sensitising. The study was performed according to OECD Guideline 406. The positive control was 2-methylol phenol (MP). After induction and challenge with ptBP, only one of 24 animals (4%) in the test group reacted positively.	Zimerson , 1999
Female Guinea Pigs	No information	20	Two studies were performed. In the first 20 guinea pigs were painted on the bar skin behind their ears with one drop of 30 % ptBP-FR in ethyl acetate daily for three weeks followed a two week rest and a second	Malten, 1967

			exposure on the left nipple with 1 % ptBP and on the right nipple with 0.5 % ptBP-FR both dissolved in ethyl acetate. Forty-eight hours later nipple biopsies were performed. Ethyl acetate had in previous experiments proven not to be noxious. Histologically 15 of 20 guinea pigs showed contact allergic reactions to the resin and 7 of these 15 animals, in addition, showed positive reactions to ptBP. The results are only described as positive or negative without any further detailed description. In the second identical study 20 white female guinea pigs were painted with one drop of 30 % ptBP and tested with one 1 % ptBP on the left nipple and with 0.5 % ptBP-FR on the right nipple. Exposure timetable as in experiment one. Fourteen guinea pigs were sensitised with ptBP and 9 of these also reacted to ptBP-FR. There was no information on how this contact allergy was scored. These studies were old, and not conducted according to current guidelines.	
Studies in humans, patch test with ptBP				
Humans	International Contact Dermatitis Research Group (ICDRG) standard test series.	6 patients allergic to cellulose ester plastics	Previous exposure is 0.5% ptBP in cellulose. Present exposure 2% ptBP in petrolateum. In this study one patient showed a positive reaction.	Jordan, 1972
Humans	Al-test and Dermicel tape	1900 patients with contact dermatitis (from the year 1974-1975)	No information regarding previous exposure. Present exposure 3% ptBP. No information regarding vehicle. In this study 1.9% patients had positive reactions.	Rudner, 1977
Humans	Al-test and Dermicel tape	900 patients with contact dermatitis (from the year 1975-1976)	No information regarding previous exposure. Present exposure 2% ptBP. No information regarding vehicle. In this study 1.1% patients had positive reactions.	Rudner, 1977
Humans	Standard Spanish contact dermatitis research group series	9 patients with severe contact leucoderma	Previous exposure was ptBP in flakes. Present exposure was 1.0% in petrolateum. All patients showed positive reactions.	Romaguera *et al*., 1981

Humans	European standard series and shoe series	1 patient with previous history of skin disease	Previous exposure ptBP or ptBP-Formaldehyd Resin (FR) from shoes. Present exposure 2% ptBP in petrolateum. In this study the patient was negative, however, after 21 she had a positive (++) reaction at the patch area. She was re-exposed 30 days later on a different patch site. At 21 days post-exposure, she developed a positive patch reaction to 2% ptBP.	Chalidapongse *et al*., 1992
Humans	ICDRG	12 patients hypersensitive to ptBP-FR	Previous exposure ptBP-FR. Present exposure 1.2% ptBP in water. All patients had negative reactions.	Zimerson, 2002
Humans	7 mm2 Patch test 12 different substances	10 shoemakers with eczema	Previous exposure was glue with ptBP. Present exposure 50% ptBP in ethylacetat. All workers showed positive reactions after 24 hours from erythema and edema or papules. After 48 hours the same symptoms were observed.	Malten, 1958
Humans	Van der Bend patch test chamber, The Netherlands using ICDRG criteria	246 (201 F, 45 M)	Previous exposure to glue with ptBP among other tings. Present exposure 2% ptBP in petrolateum. All showed negative reactions to ptBP.	Mancuso, 1996
Humans	ICDRG	359 patients suspected to have occupational skin disease	Previous exposure was allergenes in glue or plastics. Present exposure 1% ptBP in petrolateum. None showed allergic reactions to the patch test, however, 3 patient (0.8%) showed irritating reactions.	Kanerva *et al*., 1999
Humans	TRUE TestTM (Pharmacia)	1 patient exposed to cosmetics	Previous exposure ptBP-FR in lip-liner. Present exposure 2% ptBP. No information regarding vehicle used. The patient showed a positive (++) allergic reaction at day 2 and 3 and the patient developed de-pigmentation at the patch site after 7 days.	Angelini *et al*., 1993
Humans	ICDRG	1966 patients with suspected contact dermatitis	Previous exposure no information. Present exposure 1% ptBP-FR or 1% ptBP. Of the 1966 patients tested 1.5% was positive to ptBP-FR and 0.15% were positive to ptBP. In a follow-up study with 30 patients positive to ptBP-FR in the fist study, 3.33% were positive to ptBP and 87% positive to ptBP-FR.	Geldof, 1989
Respiratory sensitization humans			A chemical industry worker with history of work-related breathlessness, a bronchial provocation test with ptBP elicited a dual asthmatic reaction. No other information was available.	Brugnami *et al*., 1982

5.5.2 Respiratory system

5.5.3 Summary and discussion of sensitisation

Skin sensitisation

Of the three animal studies reported, two are negative and one is positive. The negative studies used the GPMT test, and were performed according to current test guidelines and GLP. The positive study is an older study and the protocol is not well described. No firm conclusions can be drawn based on the animal studies. However, based on the scientific quality of the studies it appears more likely that p-tert-butylphenol does not cause skin sensitisation in animals.

P-tert-butylphenol has been reported to be the first allergen identified in ptBP-FR (p-tert-butylphenolformaldehyde resin) (Zimerson and Bruze in Kanerva *et al*.; Handbook of Occupational Dermatology, 2000). There are several sensitisation studies performed using patch tests of patients with either work related contact allergy or general allergy. Furthermore, many case reports were found in the literature. Many of them used ptBP-FR and are of limited value in evaluating a possible sensitisation potential for p-tert-butylphenol. The results from these studies/reports give a very variable picture of human sensitisation to p-tert-butylphenol. In Contact Dermatitis of Fisher, 1986, (p. 649) it is stated that in the 1950s and 1960s an excess of free p-tert-butylphenol was present in the resin. Sensitisation studies indicate that an allergic reaction to the resin is frequently caused by a reaction to both the resin itself (PTBPFR) and to the free p-tert-butylphenol. It was also recommended to eliminate the excess of free p-tert-butylphenol in the resin by Malten *et al.* (1958) based on a study on shoemakers exposed to ptBP-FR/ptBP resin containing glue. Thus, earlier human exposure was more likely to have higher levels of free ptBP than current exposure, which consists of lower levels of free ptBP and more of the intermediate and degradation products (Fisher, 1986). Accordingly, patients now allergic to ptBP-FR commonly do not react to free ptBP and rarely to free formaldehyde (F). Studies performed before changing the production process are expected to reflect allergic reaction to free p-tert-butylphenol and are of more importance when assessing the sensitisation potential of ptBP than studies performed later with ptBP-FR (Rudner, 1977; Romaguera *et al.*, 1981).

It is concluded that human data on p-tert-butylphenol on skin sensitisation was derived from an old test protocol with a significant risk of misdiagnosis. Other studies according to modern protocols and standards showed no effect.

The database for assessing skin sensitisation for p-tert-butylphenol has limitations. The animal data are of varying reliability and are not sufficient to draw any conclusions of p-tert-butylphenol as a sensitiser. The human data are also of limited value since most of the studies shows very few positive results and they are mainly performed on patients with former skin allergy or other skin diseases or there is limited information about the exposure substance.

Conclusion:

It is concluded that the data does not fulfill the classification criteria.

Respiratory sensitisation

Not evaluated.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

Table 9: Repeated dose toxicity, oral

Species	Dose mg/kg body weight, mg/kg diet	Duration of treatment	Observations and Remarks	Ref.
Sprague-Dawley rats (5/sex/group)	0, 250, 500 and 1000 mg/kg bw/day by oral gavage	14-days range finding study	Noisy respiratory sound (stridor) and respiratory difficulties was observed in all dose groups. Two of 5 females and 1 of 5 males in the highest dose group died up to day 9. At this time, all survivors were killed but no signs of toxicity were observed by necropsy. At 500 mg/kg bw/day the only abnormalities reported was noisy respiratory sound in 3 of 5 animals of both sexes. The abnormal respiratory sound increased gradually during the treatment period. At 250 mg/kg bw/day, 1 of 5 females showed noisy respiratory sound. Respiratory distress was also observed at the highest dose (200 mg/kg bw/day) used in the main study described below.	MHW, Japan, 1996
Sprague-Dawley rats (13/sex/group	0, 20, 60, 200 mg/kg bw/day by oral gavage	OECD Combined Repeated Dose and Reproductive Toxicity Screening test (OECD Test Guideline 422). 44 days in males and from 14 days before mating to day 3 of lactation in females.	At 200 mg/kg bw/day one female was found dead on day 43, however, this was considered to be due to an administration mistake. Some females of the highest dose group showed stridor, associated with dyspnea (abnormal respiration). The respiratory stress observed was considered to be caused by irritation of the respiratory tract during administration. However, histopathological examinations did not reveal signs of irritation of the respiratory tract. The mean plasma concentration of albumin in the males was slightly lower in the 60 and 200 mg/kg dose groups (6 % and 13 %), accompanied by decrease in plasma protein in the 200 mg/kg bw/day males (6 %). A significant lower mean red blood cell count (5 %), and higher mean white blood cell count (38 %) in males in the 200 mg/kg bw/day dose group was also reported. No compound related morphological changes were observed during pathological	MHW, Japan, 1996

			examination of parental animals. In males there was a slight (less than 5 %) increase in mean relative liver weight. Based on respiratory distress in exposed females and effects on several blood parameters in males, the NOAEL in parental animals is considered to be 60 mg/kg bw/day. Admittedly, the severity of the systemic toxicity observed is questionable. However, in the absence of a proper repeated dose toxicity study systemic toxicity of ptBP is insufficiently addressed. This study was performed according to GLP.	
Male Syrian Golden Hamsters (15)	1.5% ptBP in the diet (approximately 1230 mg/kg bw/day)	20 weeks	The study addressed the effects of phenolic compounds, including ptBP, on the induction of proliferative lesions of the fore stomach and glandular stomach in hamsters. In this study the average body weight was slightly decreased (5 %) compared to the control group. The relative liver weight was increased by approximately 20 %. PtBP induced an incidence rate of 100% (15/15) mild, 80% (12/15) moderate, and 73.3% (11/15) severe hyperplasia and 46.7% (7/15) papillomatous lesions. The background control data for hyperplasia after exposure to basal diet was 46.7% (7/15) mild hyperplasia, 6.7% (1/15) moderate hyperplasia and 0% with severe hyperplasia.	Hirose, 1986

5.6.2 Repeated dose toxicity: inhalation

No data available.

5.6.3 Repeated dose toxicity: dermal

No data available.

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

No repeated dose toxicity study according to current Guidelines, OECD 407 (Repeated dose 28-day oral toxicity study in rodent) or OECD 408 (Repeated dose 90-day oral toxicity study in rodent) is available for p-tert-butylphenol. The only study available is an OECD combined

Repeated dose and reproductive/developmental toxicity screening test (OECD Guideline 422). The highest dose tested in the study was 200 mg/kg bw/day, and was considered a LOAEL value from this study for systemic toxicity. The NOAEL was 60 mg/kg bw/day. The NOAEL/LOAEL values were based on respiratory distress in exposed females and on effects on several blood parameters in males.

Long-term exposure to high doses of p-tert-butylphenol in the diet induced moderate effects on relative kidney and liver weights.

Conclusion:
Based on the available data no classification for repeated dose toxicity is warranted.

5.7 Mutagenicity

5.7.1 In vitro data

Table 10: Mutagenicity, in vitro

Test	Species	Conc. (mg/l)	Metabolic activity	Observations and Remarks	Ref.
Bacterial reverse mutation assay (Ames test)	*S. Typhimurium*, strains TA 98, TA 100, TA 1535 and TA 1537 as well as *Escherichia coli* WP2 *uvr*A	0, 15.6, 31.3, 62.5, 125 and 500 μg/plate for the TA strains and 0, 31.3, to 1000 μg/plate for the WP2 strain.	+/- S9 mix	The test was performed according to OECD Guideline 471/472, and according to GLP. Three plates per concentration were used, and all tests were performed in duplicate. No gene mutations were reported. The cytotoxic concentration for bacteria in the presence of metabolic activation was 500 μg/plate for all five strains; while without metabolic activation it was 500 μg/plate for TA100, TA1535, TA1537 and 1000 μg/plate for WP2 and TA98.	OECD, SIDS, 2000
Bacterial reverse mutation assay (Ames test)	*S. Typhimurium*, strains TA 98, TA 100, TA1 535 and TA 1537 as well as *Echerichia coli* WP2 *uvr*A	**First test**: 0, 1.6, 8, 40, 200, 1000 μg/plate **Second test**: 0, 31.25, 62.5, 1125, 250, 500, 1000 μg/plate	+/- S9 mix	No genotoxicity was reported up to 1000 μg/plate in both tests. Cytotoxicity was reported at 1000 μg/plate. The study was performed according to GLP.	Dow Project No: 44/901 unpublished, 1992a
Bacterial reverse	*S. Typhimurium*,	0, 125, 250, 500,	+/- S9	No genotoxicity was reported up	Dean *et*

mutation assay (Ames test)	strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 as well as *Echerichia coli* WP2, and WP2 *uvr*A	1000, 2000, and 4000 μg/plate	mix	to 4000 μg/plate. No information regarding cytotoxicity was available. The experiments were performed in triplicate or quadruplicate.	*al*., 1995
Mammalian cell mutation	Mouse lymphoma L5178Y TK(±)	**Preliminary cytotoxicity test:** 0, 5, 10, 20, 40, 80 μg/ml **Mutagenicity test**: 0, 5, 10, 20, 40, 60 μg/ml	+/- S9 mix	The study was performed according to OECD Guideline 476 and following GLP. No increase in mutant frequency was reported. Cytotoxicity was reported at 80 μg/ml.	Dow Project No. 44/902 unpublished, 1992c
Mammalian cell mutation	Mouse lymphoma L5178Y TK(±)	**Preliminary test:** 0, 20, 40, 60, 80 μg/ml exposure 3-6 hours **Secondary test**: 0, 20, 40, 60, 80 μg/m exposure 24 hours	+/- S9 mix	No increase in mutant frequency was reported following 3-6 hour exposure, either with or without metabolic activation. Following a 24-hour exposure period an increase in mutant frequency was reported. However, the mutagenic potential was investigated up to a sufficient cytotoxic condition (<20 % relative survival (RS) as a rule) and at 40μg/ml ptBP the RS was less than 20 %. Each experiment was performed with a single culture per treatment without S9 mix. The test was not performed according to the OECD TG 476. The actual mutant frequencies obtained following 24-hour exposure was for 30 μg/ml about 100 MF(x 10^{-6}), 40 μg/ml about 150 MF(x 10^{-6}) and 50 μg/ml about 230 MF(x 10^{-6}). (The actual concentrations appear to be different than from those reported above, since these concentrations are extracted visually from a figure and were not consistent with the exposure doses).	Honma *et al*., 1999
Chromosomal aberrations (CA)	Chinese Hamster Lung/IU cells (CHL/IU)	**- S9 (continous treatment, 24 or 48 hours)**: 0,	+/- S9 mix	Cytotoxicity was detected for continuous treatment at 0.025 mg /ml and for short-term treatment at 0.08 mg ptBP/ml both without metabolic activation. There was no	OECD, SIDS, 2000

		0.013, 0.025, and 0.05 mg/ml. **-S9 (short term treatment, 6 hours)**: 0, 0.02, 0.04, 0.08mg/ml . +S9 (short term treatment, 6 hours): 0, 0.013, 0.025, 0.05 mg/ml.		observation of cytotoxicity with metabolic activation. The lowest concentration producing CA was: (1) -S9 (continuous treatment) using 0.025 mg/ml (polyploidy), (2) -S9 (short-term treatment) 0.02 mg/ml (polyploidy), (3) +S9 (short-term treatment) 0.013 mg/ml (clastogenicity) and 0.025 mg/ml (polyploidy). After 24 hours the percent polyploidy was 7.63 and after 48 hours 93.18. Further evaluation of the study was not possible since only an English summary was available, the full study report being in Japanese. The study was conducted according to OECD Guideline 473, following GLP. The purity of the test substance was reported to be 99.9 %. Cytotoxicity was observed at 0.025 mg ptBP/ml (without metabolic activation, continuous treatment) and 0.08 mg ptBP/ml (without metabolic activation, short-term treatment).	
Chromosomal Aberrations (CA)	Chinese Hamster Lung/IU cells (CHL/IU)	100 to 1000 mM (from the paper the range was from 50 mg/ml to 500 mg/ml dissolved in DMSO or acetone	+/- S9 mix	ptBP induced CA and polyploidy in CHL/IU cells. The experimental concentration and solvent used is not clearly described in the publication. Therefore the concentration might be 100 mM (15mg/ml) or 50 mg/ml in water. In order to examine a possible role of metabolic activation of ptBP, the proliferating cells were treated with ptBP for 6 hours in serum-free medium with or without S9 mix, then further cultured for 18 hours in fresh medium with serum. The cells were also treated with ptBP for 24 hours and 48 hours continuously in the absence of S9 mix. Duplicate cultures were used for each experiment. The study was conducted according to OECD TG 473. ptBP induced structural chromosomal aberrations (within the rang of <20 % to =>20 %) with the	Kusakabe *et al*., 2002

				minimum effective dose manifesting severe cytotoxicity (50 % or less) in a short-term treatment assay with S9 mix, and 93.2 % polyploidy in a 48 hour continuous treatment test.	
Chromosomal aberrations (CA)	Rat lymphocytes **Initial** test: 0, 15.63, 31.25, 62.5, 125, 250 and 500 μg/ml. First test: 0, 15.63, 31.25, 62.5 μg/ml, 20 hours exposure –S9 or 4 hours exposure +S9 followed by a 16 or 20 hours expression period. Second test: 0, 3.9, 7.8, 15.63, 31.25 μg/ml, +/- S9, 20 hours and 30 hours post-treatment cell harvest.	-	+/- S9 mix	The study was performed according to OECD Guideline 473. Partial or complete haemolysis was reported at 125, 250 and 500 μg/plate and insufficient or no metaphases were available for evaluation on at least four of the six concentration levels. In the first and second test no increase in CA was reported.	Dow Project No. 44/903 unpublished, 1992b
Mitotic recombination	*Saccaromyces cerevisia* JD1	5% solution of ptBP	+/- S9 mix	No mitotic recombination was reported following exposure for 18 hours at 30 C°. One stationary and one log-phase conversion assay was performed. The test was performed according to EC Annex B16.	Dean *et al*., 1985
Cromosomal aberrations (CA)	Cultured rat liver cell line	5% solution of ptBP		No induction of CA was reported.	Dean *et al*., 1995

5.7.2 In vivo data

Table 11: Mutagenicity, in vivo

Test	Species	Conc. (mg/l)	Metabolic activ.	Observations and Remarks	Ref.
In vivo micronucleus	Mammalian bone marrow cells	24 and 48 hours		The test was performed according to OECD Test Guideline 474. ptBP was dissolved in 0.5 % methyl	MHW, Japan, in progress

test		after i.p, injection of ptBP: 12.5 mg/kg, 25 mg/kg, 50 mg/kg		cellulose. In a preliminary range-finding experiment 5 males and 5 females were exposed to 25, 50, 100 and 200 mg/kg ptBP. All animals died at 200 mg/kg, and 3 males and 4 females died at 100 mg/kg with severe clinical signs. Based on this preliminary study maximal tolerable dose (MTD) was considered to be 50 mg/kg. In the main study a single i.p. injection of ptBP was given to male CD-1 mice (5/animals/dose). 2000 PCEs of bone marrow cells was counted at 24 and 48 hours after the injection ptBP. No significant differences in signs of toxicity between negative control and ptBP-exposed animals were found. The ptBP-exposed male mice showed low locomotor activity at 25 and 50 mg/kg. No increase in the frequency of micronucleated bone marrow cells was observed in any dose groups at 24 and 48 hours after injection of ptBP compared to control animals. Based on these results, ptBP was considered not genotoxic *in vivo.*	expected in 2003

5.7.3 Human data

No data available.

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

P-tert-butylphenol was shown to be non-mutagenic in all available bacterial tests. The mouse lymphoma TK+/-locus assays have given both negative and positive results, apparently depending upon duration of exposure. However, it is important to be aware that the positive *in vitro* TK+/- test was not GLP-certified, whereas the negative *vitro* TK+/- test was. p-tert-butylphenol induced chromosomal aberrations with exogenous metabolic activation and polyploidy with and without exogenous metabolic activation in two studies with Chinese hamster lung cells but was negative in a study with rat lymphocytes, and in a study with a cultured rat-liver cell line. Thus, the overall results regarding mammalian cell mutagenicity *in vitro* is inconclusive.
No response was reported in preliminary results from an unpublished *in vivo* micronucleus test with mice. These *in vivo* studies have, however, limited value due to the absence of cytotoxicity in the target tissue or lack of information in this aspect.

Conclusion:
Based on the available data no classification for mutagenicity according to CLP criteria is proposed.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

Table 12: Carcinogenicity, oral

Species	Dose mg/kg body weight, mg/kg diet	Duration of treatment	Observations and Remarks	Ref.
Male Fisher rats (15 or 20/group)	1.5% ptBP in the diet (approximately 600 mg/kg bw/day). Pre-treatment once with 150 mg/kg bw MNNG by oral gavage and afterwards 1.5% ptBP in the diet for 51 weeks	51 weeks	This study also addressed the effect of ptBP on the induction of proliferative lesions of the forestomach and glandular stomach. The results from the group only receiving ptBP included decreased average body weight, and an approximately 8 % decrease in relative liver weight and 13 % increase in relative kidney weight. 14/15 animals showed forestomach hyperplasia, and one papilloma was reported (no hyperplasia or papilloma was reported in the negative control group). In the group pre-treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) a decrease in body weight and an increase in relative liver and kidney weight was reported. All animals showed hyperplasia in the forestomach (animals treated with MNNG and ptBP and animals only treated with MNNG). In 19/20 rats treated with MNNG and ptBP papillomas were reported (13/19 rats treated only with MNNG). In 8/20 MNNG and ptBP reated rats carcinoma "in situ" were reported (11/19 rats treated only with MNNG). Squamous cell carcinomas were reported in 15/20 rats treated with MNNG and ptBP (5/19 rats treated only with MNNG). All these observations were in the forestomach.	Hirose, 1988

5.8.2 Carcinogenicity: inhalation

No data available.

5.8.3 Carcinogenicity: dermal

No data available.

5.8.4 Carcinogenicity: human data

No data available.

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

Based on the results from the Hirose (1988) rat study where only one papilloma of the forestomach was found, and the uncertain mutagenic effects, it is considered unlikely that p-tert-butylphenol is a human carcinogen. However, its ability to increase the frequency of squamous cell carcinomas in the rat forestomach following initiation with MNNG indicates that p-tert-butylphenol may act as a tumour promoter in rats. Whether or not it may be a promoter in humans needs to be clarified. Though p-tert-butylphenol apparently is not a mutagen, the underlying database is not very solid.

The data available does not indicate a carcinogenic activity for p-tert-butylphenol. However, the available information is not sufficient to address its carcinogenic properties.

Conclusion:

No classification for carcinogenicity is proposed.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

Table 13: Reproduction, effects on fertility

Species	Route	Dose	Exposure time (h/day)	Number of generations exposed	Observations and Remarks	Ref.
Sprague-Dawley rats (13/sex/ group)	Oral by gavage	0, 20, 60 and 200 mg/kg bw/day	OECD Combined Repeated Dose Reproductive Toxicity Screening test (OECD Guideline 422). Approximately 4 weeks	1 generation	For systemic toxicity, see section 4.2.1, Repeated or prolonged toxicity. As regard effects on fertility no significant difference was reported in the number of corpora lutea, number of implantation sites, in the number of pups born, delivery index, number of pups alive, birth index, and live birth index between the control	MHW, Japan, 1996

			exposure in males and in females from 14 days before mating to day 3 of lactation.		animals and the exposed animals. There were no treatment related toxic effects in pregnant and lactating females other than respiratory irritation (see section 4.1.2). The NOAEL for effects on fertility was ≥ 200 mg/kg bw/day. The NOAEL for systemic toxicity in the parental animals was 60 mg/kg bw/day.	
Sprague Dawley rats F0: 28/sex/ group F1: 24 sex/ group	Oral in diet	0, 800, 2500 and 7500 ppm corresponding to approximately 70, 200 and 600 mg/kg/ day	OECD Test Guideline 416, US EPA Guideline OPPTS 870.3800	2 generations	Description below *	Clubb and Jardine, 2006

* **F 0 generation:** No treatment related clinical signs were reported. There were no clear effects of treatment on mating performance, fertility or duration of gestation in the F0 generation. A statistically significant decrease in body weight gain was reported in F0 males from week 0 to16 of the study at 2500 ppm (324 vs 351g in controls) and at 7500 ppm (252 vs 351g in controls), and in F0 females at 2500 ppm (95 vs 114g in controls) and at 7500 ppm (78 vs 114g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (372 vs 441g in controls), and the body weight gain was 108 vs 138g in controls. The body weight during lactation at 7500 ppm was 321 vs 353g in controls. No statistically significant changes in body weights were reported at 800 ppm in males and females.

From 2500 ppm a statistically significant reduction in food consumption was reported. For further details, see the description of the Clubb and Jardine, 2006 study in the developmental toxicity section.

At 7500 ppm in F0 females an increase in the incidence of primordial follicles (120 ± 53 vs 102 ± 44 in controls) with a concurrent decrease in the incidence of growing follicles (80 ± 29 vs 96 ± 30 in controls) was reported, however this effect was more pronounced in the F1 generation. Furthermore, F0 females at 7500 ppm had a statistically significant increase in atrophy of the vaginal epithelium with 12/28 rats affected and the severity of the findings was 5 with minimal atrophy and 7 with mild atrophy. At 2500 ppm 7/28 females had atrophy of the vaginal epithelium and the severity of the findings was 3 with minimal atrophy and 4 with mild atrophy. At 800 ppm 2/28 had minimal atrophy of the vaginal epithelium, and 1/28 in the control group with minimal atrophy. In F0 females at 7500 ppm there was a statistically significant higher incidence of females that were in pro-esterus (14 vs 6 in controls), and a lower incidence of females in meto-estrus (2 vs 13 in controls). In F0 males no significant effects on sperm motility, sperm count or sperm morphology were reported. No statistically significant effects on implantation, litter size and litter weights were reported at 800 ppm. At 7500 ppm a slight decrease in the number of implantation

sites (13.1 ± 2.0 vs 14.4 ± 3.1 in controls) and live pups born/litter (12.2 ± 2.0 vs 13.1 ± 2.8 in controls) were reported. The litter size was slightly smaller compared to controls (12.3 ± 2.0 vs 13.4 ± 3.0 in controls), and the litter weight was lower than controls at 7500 ppm (Lactation day (LD) 1: 72 ± 14 vs 80 ± 12g in controls, and LD 21: 424 ± 102 vs 598 ± 79g in controls). Litter weight gain was similarly affected. At 2500 ppm pup body weights and litter weights were also reduced from LD 14 (324 ± 83 vs 357 ± 52g in controls). In addition at 7500 ppm pup survival was reduced particularly over days 1-4 of lactation where 6 different litters had more than 3 pups dying, and in 2 of these litters all pups died.

At 7500 ppm a statistically significant increase in the weights of the kidneys (4.29 vs 3.96 g in controls) and liver (20.19 vs 18.87 g in controls) in males was reported, and in females a statistically significant decrease in the weight of the adrenal gland (0.064 vs 0.076 g in controls), ovaries (0.081 vs 0.107 g in controls) and pituitary gland (0.011 vs 0.012 g in controls) were reported following covariance analysis with the body weight as the covariate. At 2500 ppm a statistically significant decrease in the weights of the adrenal gland (0.070 vs 0.079g in controls) and ovaries (0.095 vs 0.109 g in controls) were reported in females. No changes in organ weights were reported at 2500 ppm in males and at 800 ppm in males and females.

F1 generation: No treatment related clinical signs were reported. There were no clear effects of treatment on mating performance, fertility or duration of gestation in the F1 generation. A statistically significant decrease in body weight gain was reported in F1 males from week 4 to 22 of the study at 7500 ppm (357 vs 442g in controls), and in F1 females from week 4 to 15 (prior to mating) at 7500 ppm (143 vs 173g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (320 vs 411g in controls). The body weight gain during gestation in F1 females at 7500 ppm was 89 vs 130g in controls. The body weight during lactation at 7500 ppm was 290 vs 335g in controls. At 2500 ppm statistically significant changes in body weights in males were reported from week 4 (114 vs 124 in controls) to week 9 (358 vs 379 in controls) of treatment. No statistically significant changes in body weights were reported at 2500 ppm in females and at 800 ppm in males and females.

From 2500 ppm in females and at 7500 ppm a statistically significant reduction in food consumption was reported.

At 7500 ppm in F1 females an increase in the incidence of primordial follicles (134 ± 55 vs 79 ± 35 in controls) with a concurrent decrease in the incidence of growing follicles (64 ± 13 vs 80 ± 30 in controls) was reported. This effect was more pronounced in the F1 generation compared to the F0 generation. In F1 females at 7500 ppm an increase in atrophy of the vaginal epithelium was reported compared to control animals, with the severity being mild in 10/24 of the animals and minimal in 4/24 of the animals, with a total of 14/24 affected. The severity in the atrophy of the vaginal epithelium was more pronounced in the F1 generation compared to the F0 generation. No increase in atrophy of the vaginal epithelium was reported at the lower doses. The severity in F1 females increased compared to F0 females. In F1 males no significant effects on sperm motility, sperm count or sperm morphology were reported. In the F1 generation the number of implantation sites (11.6 ± 1.3 vs 14.4 ± 1.9 in controls at 7500 ppm) and live pups born/litter (10.8 ± 1.8 vs 13.5 ± 2.6 in controls at 7500 ppm) was much more variable compared to the F0 generation, however, the survival of these smaller litters was normal. After LD 1 pup body weight was lower than controls (62 ± 9 vs 78 ± 14 in controls), and by LD 21 the body weight was approximately 25 - 30% lower than control weights (395 ± 51 vs 554 ± 146 in controls). Litter weight gain was similarly affected. At 7500 ppm vaginal opening and preputial separation occurred 3 and 4 days later than controls, respectively. The weight of the female pups at vaginal opening was 120 ± 13 in controls and 122 ± 11 at 7500 ppm, and in male pups at preputial separation 220 ± 20 in controls and 205 ± 20 at 7500 ppm. The effect on preputial separation may be related to the lower body weights of the male pups. No effects on anogenital distance and nipple retention were reported.

At 7500 organ weight changes in weanling animals included a decreased spleen weight in males (0.26 vs 0.29 g in controls) and females (0.24 vs 0.27 g in controls) at 7500 ppm following covariance analysis with the body weight as the covariate. Furthermore, in F1 females at 7500 ppm statistically significant decreases in the weights of the adrenal gland (0.059 vs 0.076 g in

controls), ovaries (0.075 vs 0.104 g in controls), pituitary gland (0.011 vs 0.013 g in controls), brain (1.84 vs 1.89g in controls), kidney (2.32 vs 2.52g in controls) and uterus (0.48 vs 0.67 g in controls) were reported when compared to controls, as well as a significant increase in liver weight (18.47 vs 16.18 g in controls) following covariance analysis with the body weight as the covariate. At 2500 ppm a statistically significant decrease in the weights of the adrenal gland (0.068 vs 0.076 g in controls) and brain (1.84 vs 1.89 g in controls) were reported in F1 females when compared to controls, and the liver weight was significantly increased (17.35 vs 16.18 g in controls) when compared to controls following covariance analysis with the body weight as the covariate. No changes in organ weights were reported at 800 ppm in males and females.

F2 generation: No effects on survival of the pups. At 7500 ppm a slightly smaller litter size and reduced litter weight was reported at LD 1. Pup weight gain was lower than controls, and at LD 20 the weight gain was 20% less than controls. At 2500 ppm the pup weight was lower than controls from LD 14, with a concurrent decrease in litter weight gain as well. The NOAEL for effects on reproductive organs/fertility was set at 800 ppm corresponding to 70 mg/kg bw/day. The NOAEL value was based on a statistically significant decrease in the relative weight of the ovary in the F0 and F1 generation from 2500 ppm, and an increase in vaginal epithelial atrophy compared to control animals from 2500 ppm in F0 females. An increase in vaginal epithelial atrophy compared to control animals was also reported in the F1 generation at 7500 ppm, and the severity of the vaginal epithelium atrophy was more pronounced in the F1 generation compared to the F0 generation.

Combined Repeated Dose Reproductive Toxicity Screening test (OECD Guideline 422).
(MHW, Japan, 1996)

Animals: Sprague-Dawley rats (13/sex/group)
Route: Oral by gavage
Dose: 0, 20, 60, 200 mg/kg bw/day
Exposure: Males 4 weeks females from 14 days before mating to day 3 of lactation.

Observations and Remarks:
For systemic toxicity, see section "Repeated dose toxicity".
For effects related to developmental toxicity, see section "Developmental toxicity".
Fertility: No significant difference was reported in the number of corpora lutea, number of implantation sites, in the number of pups born, delivery index, number of pups alive, birth index, and live birth index between the control animals and the exposed animals.
There were no treatment related toxic effects in pregnant and lactating females other than respiratory irritation (see section 4.1.2).
The NOAEL for effects on fertility was ≥ 200 mg/kg bw/day. The NOAEL for systemic toxicity in the parental animals was 60 mg/kg bw/day.

Two generation reproduction toxicity study. OECD Test Guideline 416, US EPA Guideline OPPTS 870.3800
(Clubb and Jardine, 2006)

Animals: Sprague Dawley rats. F0: 28/sex/group. F1: 24 sex/group
Route: Oral in diet
Dose: 0, 800, 2500 and 7500 ppm corresponding to approximately average dose of 70, 200 and 600 mg/kg/day.

The estimated dose along the time of the study is indicated in the Tables below. During some specific periods of the live, the actual average dose of the group was higher than the "limit dose" of 1000 mg/Kg bw/day. This occurred for the groups at the high dose (7500ppm) as follows:

Males F1 generation: weeks 5 and 6 (1221 and 1013 mg/kg bw/day)

Females F0 generation: last 2-3 weeks of lactation (1353 and 1788 mg/kg bw/day
Females F1 generation: first 5-6 weeks (1220, 1033 mg/kg bw/day)
Females F1 generation: last 2-3 weeks of lactation (1525 and 1814 mg/kg bw/day)

Values in the range of 800-988 mg/kg bw/day were also observed in F1 males week 7 and in females (F0) week 3 of gestation and week 1 of lactation and F1females week 7 of gestation and week 1 of lactation.

In the group of 800-1000 and 2500 ppm, average doses did not exceed the limit dose of 1000 mg/kg bw/day

Table 14: MALES F0 generation Achieved dosages of ptBP (mg/kgbw/day) (from original study)

Week	800 ppm	2500 ppm	7500 ppm
1	91	265	611
2	80	242	729
3	71	214	607
4	68	215	679
5	62	190	564
6	58	184	563
7	57	181	549
8	54	169	529
9	52	162	508
10	52	165	496
12	48	155	503
13	48	151	491
14	46	138	444
15	45	143	450
16	44	140	440

Table 15: MALES F1 generation Achieved dosages of ptBP (mg/kgbw/day) (from original study)

Week	800 ppm	2500 ppm	7500 ppm
5	126	395	**1,221**
6	105	324	**1,013**
7	91	282	889
8	74	232	737
9	67	208	684
10	65	203	637
11	63	194	636
12	58	187	578
13	60	188	590
14	56	177	569
15	56	178	573
18	48	155	508
19	49	154	511
20	46	148	493
21	48	155	503
22	45	133	429

Table 16: FEMALES F0 generation Achieved dosages of ptBP (mg/kgbw/day) (from original study)

Week	800 ppm	2500 ppm	7500 ppm
1	84	227	537
2	76	227	656
3	70	216	689
4	72	228	661
5	72	210	607
6	70	204	607
7	65	197	578
8	65	203	579
9	62	199	584
10	62	194	571
Week of Gestation			
1	72	204	573
2	69	222	608
3	81	258	804
Week of Lactation			
1	99	300	865
2	164	493	**1,353**
3	204	626	**1,788**

Table 17: FEMALES F1 generation Achieved dosages of ptBP (mg/kgbw/day) (from original study)

Week	800 ppm	2500 ppm	7500 ppm
5	126	398	**1,220**
6	109	344	**1,033**
7	92	285	858
8	84	251	771
9	81	256	768
10	82	250	731
11	73	221	670
12	73	233	688
13	71	215	651
14	71	217	645
15	68	204	617
Week of Gestation			
1	69	212	629
2	67	218	632
3	67	218	667
Week of Lactation			
1	111	306	988
2	175	525	**1,525**
3	227	643	**1,814**

F0 generation:

Clinical signs: No treatment related clinical signs were reported.

Mating-Fertility-Gestation: There were no clear effects of treatment on mating performance, fertility or duration of gestation in the F0 generation at any dose.

Body weight: A statistically significant decrease in body weight gain was reported on week 1 to

16 at 7500 ppm exposure during lactation and gestation. No statistically significant changes in body weights were reported at 800 ppm in males and females.

Week 1-16	Males	Females	F lactation	F gestation
Control	351	114	353	441
2500		85		85
7500	252	78	321	372

Food consumption: From 2500 ppm a statistically significant reduction in food consumption was reported. See developmental toxicity section.

Primordial follicles: At 7500 ppm in F0 females an increase in the incidence of primordial follicles (120 ± 53 vs 102 ± 44 in controls) with a concurrent decrease in the incidence of growing follicles (80 ± 29 vs 96 ± 30 in controls). This effect was more pronounced in the F1 generation.

Atrophy of the vaginal epithelium: F0 females at 7500 ppm had a statistically significant increase (12/28 rats affected); Severity: 5 animals with minimal atrophy and 7 with mild atrophy.
At 2500 ppm: (7 of 28) there were 3 animals with minimal and 4 with mild atrophy.
At 800 ppm 2/28 animals had minimal atrophy, and 1/28 in the control group had minimal atrophy.

Proestrus versus metestrus: F0 females at 7500 ppm: There was a statistically significant higher incidence of females that were in pro-estrus (14 vs 6 in controls), and a lower incidence in metoestrus (2 vs 13 in controls).

Sperm quality: In F0 males no significant effects on sperm motility, sperm count or sperm morphology were reported.

Implantations, litter size and litter weight, survival: 800 ppm: no statistically significant effects on implantation, litter size and litter weights. At 7500 ppm litter weight was lower than controls at Lactation day (LD) 1 and LD 21. Litter weight gain was similarly affected. At 2500 ppm pup body weights and litter weights were also reduced from LD 14 (324 ± 83 vs 357 ± 52g in controls).

	Implantation sites	Live pups born/litter	Litter size	Litter weight (g) LD1	weight (g) LD14	Litter weight (g) LD21
Control	14.4±3	13,1+2.8	13.4+3.0	80+12	357+52	598+79
2500					324+83	
7500	13,1±2	12.2+2	12.3+2.0	72+14		424+102

At 7500 ppm pup survival was reduced particularly over days 1-4 of lactation where 6 different litters had more than 3 pups dying, and in 2 of these litters all pups died.

Pup findings: Males at 7500 ppm showed a statistically significant increase in the weights of the kidneys and liver. Females at 7500 ppm showed statistically significant decrease in the weight of the adrenal gland, ovaries and pituitary gland following covariance analysis with the body weight as the covariate. At 2500 ppm a statistically significant decrease in the weights of the adrenal gland and ovaries was observed. No changes are observed at 2500 ppm in males and at 800 ppm in males and females.

	7500	2500	800	Control

Male				
Kidney	4,29g	-	-	3.96g
Liver	20.19g			18.87 g
Female				
Adrenal gland	0,064g	0.070 g		0.076 g
Ovaries	0.081g	0.095g		0.107 g
Pituitary gl.	0.011g			0.012 g

F1 generation:

Clinical signs: No treatment related clinical signs were reported.

Mating-Fertility-Gestation: There were no clear effects of treatment on mating performance, fertility or duration of gestation in the F1 generation.

Body weight: A statistically significant decrease in body weight gain was reported in F1 males from week 4 to 22 of the study at 7500 ppm (357 vs 442g in controls), and in F1 females from week 4 to 15 (prior to mating) at 7500 ppm (143 vs 173g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (320 vs 411g in controls). The body weight gain during gestation in F1 females at 7500 ppm was 89 vs 130g in controls. The body weight during lactation at 7500 ppm was 290 vs 335g in controls.

At 2500 ppm statistically significant changes in body weights in males were reported from week 4 (114 vs 124 in controls) to week 9 (358 vs 379 in controls) of treatment. No statistically significant changes in body weights were reported at 2500 ppm in females and at 800 ppm in males and females.

Food consumption: From 2500 ppm in females and at 7500 ppm a statistically significant reduction in food consumption was reported.

Primordial follicles: At 7500 ppm in F1 females an increase in the incidence of primordial follicles (134 ± 55 vs 79 ± 35 in controls) with a concurrent decrease in the incidence of growing follicles (64 ± 13 vs 80 ± 30 in controls) was reported. This effect was more pronounced in the F1 generation compared to the F0 generation.

Atrophy of the vaginal epithelium: In F1 females at 7500 ppm an increase in atrophy of the vaginal epithelium was reported compared to control animals, with the severity being mild in 10/24 of the animals and minimal in 4/24 of the animals, with a total of 14/24 affected. The severity in the atrophy of the vaginal epithelium was more pronounced in the F1 generation compared to the F0 generation. No increase in atrophy of the vaginal epithelium was reported at the lower doses. The severity in F1 females increased compared to F0 females.

Sperm quality: In F1 males no significant effects on sperm motility, sperm count or sperm morphology were reported.

Implantations, litter size and weight, survival: In the F1 generation the number of implantation sites (11.6 ± 1.3 vs 14.4 ± 1.9 in controls at 7500 ppm) and live pups born/litter (10.8 ± 1.8 vs 13.5 ± 2.6 in controls at 7500 ppm) was much more variable compared to the F0 generation, however, the survival of these smaller litters was normal. After LD 1 pup body weight was lower than controls (62 ± 9 vs 78 ± 14 in controls), and by LD 21 the body weight was approximately 25 - 30% lower than control weights (395 ± 51 vs 554 ± 146 in controls). Litter weight gain was similarly affected.
Pup findings: At 7500 ppm vaginal opening and preputial separation occurred 3 and 4 days later than controls, respectively. The weight of the female pups at vaginal opening was 120 ± 13 in controls and 122 ± 11 at 7500 ppm, and in male pups at preputial separation 220 ± 20 in controls and 205 ± 20 at 7500 ppm. The effect on preputial separation may be related to

the lower body weights of the male pups. No effects on anogenital distance and nipple retention were reported.

At 7500 organ weight changes in weanling animals included a decreased spleen weight in males (0.26 vs 0.29 g in controls) and females (0.24 vs 0.27 g in controls) at 7500 ppm following covariance analysis with the body weight as the covariate. Furthermore, in F1 females at 7500 ppm statistically significant decreases in the weights of the adrenal gland (0.059 vs 0.076 g in controls), ovaries (0.075 vs 0.104 g in controls), pituitary gland (0.011 vs 0.013 g in controls), brain (1.84 vs 1.89g in controls), kidney (2.32 vs 2.52g in controls) and uterus (0.48 vs 0.67 g in controls) were reported when compared to controls, as well as a significant increase in liver weight (18.47 vs 16.18 g in controls) following covariance analysis with the body weight as the covariate.

At 2500 ppm a statistically significant decrease in the weights of the adrenal gland (0.068 vs 0.076 g in controls) and brain (1.84 vs 1.89 g in controls) were reported in F1 females when compared to controls, and the liver weight was significantly increased (17.35 vs 16.18 g in controls) when compared to controls following covariance analysis with the body weight as the covariate.

No changes in organ weights were reported at 800 ppm in males and females.

F2 generation:
Implantations, litter size and weight, survival: No effects on survival of the pups.
At 7500 ppm a slightly smaller litter size and reduced litter weight was reported at LD 1. Pup weight gain was lower than controls, and at LD 20 the weight gain was 20% less than controls.

At 2500 ppm the pup weight was lower than controls from LD 14, with a concurrent decrease in litter weight gain as well.

NOAELs: The NOAEL for effects on reproductive organs/fertility was set at 800 ppm corresponding to 70 mg/kg bw/day. The NOAEL value was based on a statistically significant decrease in the relative weight of the ovary in the F0 and F1 generation from 2500 ppm, and an increase in vaginal epithelial atrophy compared to control animals from 2500 ppm in F0 females.

An increase in vaginal epithelial atrophy compared to control animals was also reported in the F1 generation at 7500 ppm, and the severity of the vaginal epithelium atrophy was more pronounced in the F1 generation compared to the F0 generation.

5.9.2 Developmental toxicity

Table 18: Reproduction, developmental toxicity

Species	**Route**	***Dose mg/kg/ day ppm** ****Conc. (mg/l)**	**Exposure time (h/day)**	**Exposure period:** **- number of generations or** **- number of days during pregnancy**	**Observations and Remarks**	**Ref.**
Sprague Dawley rats F0: 28/sex/	Oral in diet	0, 800, 2500 and 7500 ppm correspon ding to approxima	OECD Test Guideline 416, US EPA Guideline OPPTS	2 generations	**F0 generation:** No treatment related clinical signs were reported. A statistically significant decrease in body weight gain was	Clubb and Jardi ne, 2006

group F1: 24 sex/ group		tely 60, 200 and 600 mg/kg/day	870.3800		reported in F0 females at 2500 ppm (95 vs 114g in controls) and at 7500 ppm (78 vs 114g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (372 vs 441g in controls), and the body weight gain was 108 vs 138g in controls. The body weight during lactation at 7500 ppm was 321 vs 353g in controls. No statistically significant changes in body weights were reported at 800 ppm in females. At 7500 ppm food consumption was statistically significant reduced in F0 females from week 1 to week 10 of treatment, prior to mating (week 1; 13.7 vs 20.6 g/animal/day in controls, week 10; 20.0 vs 22.8 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F0 females was 30.4 vs 33.0 g/animal/day in controls, and during lactation 75.8 vs 91.6 g/animals/day in controls. At 2500 ppm in females a statistically significant reduction in food consumption was reported in 6 of 10 weeks of treatment, prior to mating (week 1; 17.5 vs 20.6 g/animal/day in controls, week 10; 21.3 vs 22.8 g/animal/day in controls). No statistically significant changes in food consumption were	

					reported at 800 ppm in females. At 7500 ppm the litter weight was lower than controls at 7500 ppm (LD 1: 72 ± 14 vs 80 ± 12g in controls, and LD 21: 424 ± 102 vs 598 ± 79g in controls). Litter weight gain was similarly affected. At 2500 ppm pup body weights and litter weights were also reduced from LD 14 (324 ± 83 vs 357 ± 52g in controls). In addition at 7500 ppm pup survival was reduced particularly over days 1-4 of lactation where 6 different litters had more than 3 pups dying, and in 2 of these litters all pups died. **F1 generation**: No treatment related clinical signs were reported. A statistically significant decrease in body weight gain was reported in F1 females from week 4 to 15 (prior to mating) at 7500 ppm (143 vs 173g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (320 vs 411g in controls). The body weight gain during gestation in F1 females at 7500 ppm was 89 vs 130g in controls. The body weight during lactation at 7500 ppm was 290 vs 335g in controls. At 7500 ppm food consumption was statistically significant reduced in F0 females from week 5 to week 15 of treatment (prior	

					to mating) (week 5; 17.4 vs 19.2 g/animal/day in controls, week 15; 19.0 vs 23.7 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F1 females was 26.2 vs 30.9 g/animal/day in controls, and during lactation 69.9 vs 91.1 g/animal/day in controls. At 2500 ppm a statistically significant reduction in food consumption was reported in females at week 13 (21.8 vs 23.1 g/animal/day in controls) and week 15 (21.9 vs 23.7 g/animal/day in controls) of treatment (prior to mating). After LD 1 pup body weight was lower than controls (62 ± 9 vs 78 ± 14 in controls), and by LD 21 the body weight was approximately 25 - 30% lower than control weights (395 ± 51 vs 554 ± 146 in controls) at 7500 ppm. Litter weight gain was similarly affected. At 7500 ppm vaginal opening and preputial separation occurred 3 and 4 days later than controls, respectively. The weight of the female pups at vaginal opening was 120 ± 13 in controls and 122 ± 11 at 7500 ppm, and in male pups at preputial separation 220 ± 20 in controls and 205 ± 20 at 7500 ppm. The effect on preputial separation may be related to the lower body weights of the male pups. No effects	

					on anogenital distance and nipple retention were reported. **F2 generation:** No effects on survival of the pups. At 7500 ppm a slightly smaller litter size and reduced litter weight was reported at LD 1. Pup weight gain was lower than controls, and at LD 20 the weight gain was 20% less than controls. At 2500 ppm the pup weight was lower than controls from LD 14, with a concurrent decrease in litter weight gain as well. The NOAEL for developmental toxicity was set at 800 ppm corresponding to 70 mg/kg bw/day from this study. The NOAEL value for offspring was based on a reduced pup body weight and litter weight from LD 14 from 2500 ppm in the F1 generation, and F2 generation. At this dose level no statistically significant reduction in maternal body weight during gestation or lactation was reported. The NOAEL for maternal toxicity was 800 ppm and was based on a statistically significant decrease in body weight gain in F0 females at 2500 ppm from week 1-16 of the study as well as a statistically significant reduction in food consumption in F0 and F1 females before mating. A statistically significant reduction in ovary weight and adrenal gland weight was also reported at	

					2500 ppm.	
Sprague-Dawley rats (13/sex/ group)	Oral by gavage	0, 20, 60and 200 mg/kg bw/day		OECD Combined Repeated Dose Reproductive Toxicity Screening test (OECD Guideline 422). Approximately 4 weeks exposure in males and in females from 14 days before mating to day 3 of lactation.	For systemic toxicity, see section 4.2.1, Repeated or prolonged toxicity. As regard effects on development examination of body weights and gross morphology of the offspring revealed no effects of ptBP, and there were no significant differences in the viability index day 4 of lactation between the control animals and the exposed animals. No treatment related toxic effects on offspring were reported and a NOAEL of ≥ 200 mg/kg/day for offspring was identified. For maternal toxicity a NOAEL at 60 mg/kg bw/day was identified based on the observation that some females showed stridor associated with dyspnea in the 200 mg/kg bw/day dose group. However, this was likely caused by irritation of the respiratory tract, and may be related to a secondary effect due to gavage application of an irritating material (for further details see section 4.1.2 repeated and prolonged exposure).	MHW, Japan, 1996

Combined Repeated Dose Reproductive Toxicity Screening test (OECD Guideline 422)
(MHW, Japan, 1996)
Animals: Sprague-Dawley rats (13/sex/group)
Route: Oral by gavage
Dose: 0, 20, 60, 200 mg/kg bw/day
Exposure: Males 4 weeks females from 14 days before mating to day 3 of lactation.

Observations and Remarks:
For systemic toxicity, see section of "Repeated dose toxicity".

For effects related with fertility, see previous section.
As regard effects on development examination of body weights and gross morphology of the offspring revealed no effects of ptBP, and there were no significant differences in the viability index day 4 of lactation between the control animals and the exposed animals. No treatment related toxic effects on offspring were reported and a NOAEL of ≥ 200 mg/kg/day for offspring was identified.
For maternal toxicity a NOAEL at 60 mg/kg bw/day was identified based on the observation that some females showed stridor associated with dyspnea in the 200 mg/kg bw/day dose group. However, this was likely caused by irritation of the respiratory tract, and may be related to a secondary effect due to gavage application of an irritating material (for further details see section 4.1.2 repeated and prolonged exposure).

Two generation reproduction toxicity study, OECD Test Guideline 416, US EPA Guideline OPPTS 870.3800
(Clubb and Jardine, 2006)

Animals: Sprague Dawley rats. F0: 28/sex/group. F1: 24 sex/group
Route: Oral in diet
Dose: 0, 800, 2500 and 7500 ppm corresponding to approximately average dose of 70, 200 and 600 mg/kg/day. The estimated dose along the time of the study is indicated in the Tables. During some specific periods of the live, the actual average dose of the group was higher than the "limit dose" of 1000 mg/kg bw/day. See details in previous section.

F0 generation:

Clinical signs: No treatment related clinical signs were reported.

Body weight: A statistically significant decrease in body weight gain was reported in F0 females at 2500 ppm (95 vs 114g in controls) and at 7500 ppm (78 vs 114g in controls).

At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (372 vs 441g in controls), and the body weight gain was 108 vs 138g in controls. The body weight during lactation at 7500 ppm was 321 vs 353g in controls. No statistically significant changes in body weights were reported at 800 ppm in females.

Food consumption: At 7500 ppm food consumption was statistically significant reduced in F0 females from week 1 to week 10 of treatment, prior to mating (week 1; 13.7 vs 20.6 g/animal/day in controls, week 10; 20.0 vs 22.8 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F0 females was 30.4 vs 33.0 g/animal/day in controls, and during lactation 75.8 vs 91.6 g/animal/day in controls.

At 2500 ppm in females a statistically significant reduction in food consumption was reported in 6 of 10 weeks of treatment, prior to mating (week 1; 17.5 vs 20.6 g/animal/day in controls, week 10; 21.3 vs 22.8 g/animal/day in controls). No statistically significant changes in food consumption were reported at 800 ppm in females.

Implantations, litter size and weight, survival: At 7500 ppm the litter weight was lower than controls at 7500 ppm (LD 1: 72 ± 14 vs 80 ± 12g in controls, and LD 21: 424 ± 102 vs 598 ± 79g in controls). Litter weight gain was similarly affected. At 2500 ppm pup body weights and litter weights were also reduced from LD 14 (324 ± 83 vs 357 ± 52g in controls). In addition at 7500 ppm pup survival was reduced particularly over days 1-4 of lactation where 6 different litters had more than 3 pups dying, and in 2 of these litters all pups died.

F1 generation:

Clinical signs: No treatment related clinical signs were reported.

Body weight: A statistically significant decrease in body weight gain was reported in F1 females from week 4 to 15 (prior to mating) at 7500 ppm (143 vs 173g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (320 vs 411g in controls). The body weight gain during gestation in F1 females at 7500 ppm was 89 vs 130g in controls. The body weight during lactation at 7500 ppm was 290 vs 335g in controls.

Food consumption: At 7500 ppm food consumption was statistically significant reduced in F0 females from week 5 to week 15 of treatment (prior to mating) (week 5; 17.4 vs 19.2 g/animal/day in controls, week 15; 19.0 vs 23.7 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F1 females was 26.2 vs 30.9 g/animal/day in controls, and during lactation 69.9 vs 91.1 g/animal/day in controls.

At 2500 ppm a statistically significant reduction in food consumption was reported in females at week 13 (21.8 vs 23.1 g/animal/day in controls) and week 15 (21.9 vs 23.7 g/animal/day in controls) of treatment (prior to mating). After LD 1 pup body weight was lower than controls (62 ± 9 vs 78 ± 14 in controls), and by LD 21 the body weight was approximately 25 - 30% lower than control weights (395 ± 51 vs 554 ± 146 in controls) at 7500 ppm. Litter weight gain was similarly affected.

Pup findings: At 7500 ppm vaginal opening and preputial separation occurred 3 and 4 days later than controls, respectively. The weight of the female pups at vaginal opening was 120 ± 13 in controls and 122 ± 11 at 7500 ppm, and in male pups at preputial separation 220 ± 20 in controls and 205 ± 20 at 7500 ppm. The effect on preputial separation may be related to the lower body weights of the male pups. No effects on anogenital distance and nipple retention were reported.

F2 generation:

Litter size and weight, survival: No effects on survival of the pups.

At 7500 ppm a slightly smaller litter size and reduced litter weight was reported at LD 1. Pup weight gain was lower than controls, and at LD 20 the weight gain was 20% less than controls.

At 2500 ppm the pup weight was lower than controls from LD 14, with a concurrent decrease in litter weight gain as well.

NOAELs: The NOAEL for developmental toxicity was set at 800 ppm corresponding to 70 mg/kg bw/day from this study. The NOAEL value for offspring was based on a reduced pup body weight and litter weight from LD 14 from 2500 ppm in the F1 generation, and F2 generation. At this dose level no statistically significant reduction in maternal body weight during gestation or lactation was reported.

The NOAEL for maternal toxicity was 800 ppm and was based on a statistically significant decrease in body weight gain in F0 females at 2500 ppm from week 1-16 of the study as well as a statistically significant reduction in food consumption in F0 and F1 females before mating. A statistically significant reduction in ovary weight and adrenal gland weight was also reported at 2500 ppm.

5.9.3 Human data

No data available.

5.9.4 Other relevant information

5.9.5 Summary and discussion of reproductive toxicity

Fertility

The results from the Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test (OECD 422) indicated that p-tert-butylphenol had no effect on fertility at the dose levels tested (0, 20, 60 and 200 mg/kg bw/day).
However, in the 2-generation reproduction study, the following effects were reported: At 7500 ppm a decreased number of implantation sites and live pups born were reported as well as slightly smaller litter size compared to controls. At 7500 ppm also an increase in atrophy of the vaginal epithelium with 12/28 rats affected in the F1 generation and 14/24 rats affected in the F2 generation were seen. Furthermore, in the F0 females at 7500 ppm an increase in the incidence of primordial follicles with a concurrent decrease in the incidence of growing follicles were reported.

Comparison with the criteria:

Criteria for Repr. 2 H361f	**Data fulfilling the criteria**
CLP Regulation 3.7.2. Hazard categories for reproductive toxicants. Category 2. Suspected human reproductive toxicant (Label H361: Suspected of damaging fertility or the unborn child) Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects. Guide 3.7.1.3: Adverse effects on sexual function and fertility Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and	There are evidences of adverse effects in fertility in experimental animals in a two generation reproduction toxicity study: Decreased number of implantation sites and live pups born were reported as well as slightly smaller litter size compared to controls. At 7500 ppm an increase in atrophy of the vaginal epithelium with 12/28 rats affected in the F1 generation and 14/24 rats affected in the F2 generation Furthermore, in the F0 females at 7500 ppm an increase in the incidence of primordial follicles with a concurrent decrease in the incidence of growing follicles were reported. As the observed effects occur only at the high dose and there is not obvious severe alteration of reproductive performance, the data does not support category 1 but category 2 is considered appropriate.

male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.	

During specific critical periods of the life of the exposed animals, the actual average dose of the group was higher than the "limit dose" of 1000 mg/kg bw/day. This occurred for the groups at the high dose (7500 ppm) as follows:

- Males in F1 generation: weeks 5 and 6 (1221 and 1013 mg/kg bw/day)
- Females in F0 generation: last 2-3 weeks of lactation (1353 and 1788 mg/kg bw/day)
- Females in F1 generation: first 5-6 weeks (1220, 1033 mg/kg bw/day)
- Females in F1 generation: last 2-3 weeks of lactation (1525 and 1814 mg/kg bw/day)

Moreover, values in the range of 800-988 mg/kg bw/day were observed in F1 males during week 7 and in F0 females during week 3 of gestation and week 1 of lactation, as well as in F1 females during week 7 of gestation and week 1 of lactation.

In the groups exposed to 800-1000 and 2500 ppm, respectively, the average doses did not exceed the limit dose of 1000 mg/kg bw/day.

As the most critical effects are observed only at the high dose (7500 ppm) at which the limit dose is exceeded during critical periods, the proposal for classification could be considered inappropriate.

However, RAC considered that classification cannot be excluded by the argument that the limit dose is exceeded as:

(1) the limit dose is exceeded only during lactation,

(2) the classification should be based on the effects seen,

(3) the limit dose is a guideline for testing and there is no cut-off value for classification according to the CLP Regulation.

Therefore based on the effects seen on fertility, RAC supports classification of p-tert-butylphenol for Reproductive toxicity, effects on sexual function and fertility, Category 2, (Repr. 2; H361f), according to the CLP Regulation.

Conclusion:

Based on the data from the 2-generation reproduction study in rats p-tert-butylphenol is proposed to be classified for fertility according to CLP criteria with Repr. 2; H361f (corresponding to Repr. Cat. 3; R62 according to Directive 67/548/EEC).

Note: Classification with Repr. Cat. 3; R62 (Repr. 2; H361f according to CLP) was agreed at TC C&L in September 2007.

Developmental toxicity

The results from the Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Test (OECD 422) indicated that p-tert-butylphenol induced no embryotoxicity or teratogenicity at the dose levels tested (0, 20, 60 and 200 mg/kg bw/day).

In the 2-generation reproduction study, the following effects were reported: A decrease in pup body weights and litter weights in the F1 generation from 2500 ppm, and a smaller litter size as well as an increase in pup mortality in the F1 generation at 7500 ppm. A delay in vaginal opening and preputial separation in the F1 generation was reported at 7500 ppm.

Conclusion:

RAC concludes that the available data are not sufficient to propose classification for developmental toxicity. This is based on the fact that no embryotoxicity or teratogenicity was induced at the tested doses in a Combined Repeated Dose and Reproductive/ Developmental Toxicity Screening Test (OECD 422), and the fact that the doses causing significant fertility effect in the 2-generation reproduction study did not caused significant developmental toxicity effects supporting classification.

5.10 Specific target organ toxicity – single exposure

5.10.1 Respiratory tract irritation

Table 19: Irritation, respiratory tract

Species	No. of animals	Exposure time (h/day)	Conc.	Observations and remarks	Ref.
Sprague-Dawley rats No guideline Acute inhalation toxicity	5 males 5 female	4 hours	5600 mg/m^3 to dust aerosols	Limit test at dynamically generated dust aerosol. Animals were exposed in a 120 liter chamber for 4 hours to ptBP as dust aerosol of 5600 mg/m3 (median particle diameter of 3.6 µm) with additional vapour component of 30 mg/m3. Dust aerosol was generated by leading vapour from melted ptBP (110 °C) to the exposure chamber where the vapour condensed in air to fine powder. Within one to two days following exposure, 1 rat of each sex died. The dead animals showed dark red or purple discoloration. No further details on severity of clinical signs of toxicity or number of animals affected are given in the report.	Klonne *et al*., 1988
Sprague-Dawley rats	5 males 5 female	4 hours	Saturated atmosphere. Actual concentrati	Rats were exposed in a static generated vapor. It was prepared putting 100g of the substance and leaving to statically saturating the	

			on not indicated.	chamber. The actual concentration in the air of the chamber is not indicated. We can assume it to be around the concentration determined by its relative vapour pressure (0.5 Pa at 20 °C) in the air close to the site of deposit of the substance and somewhat lower in the whole chamber. No effects were observed in the rat exposed in this chamber during 6 hour exposure. There were no effect on body weight and no signs of toxicity following clinical observation and necropsy. No respiratory effects are indicated. Another similar study is mentioned in the RAR with 8 h exposure (BASF 1971) with no observed effects. No details are indicated.	
Rats	13 males 13 females	This study was a OECD combined repeated dose toxicity and reproductive/developmental toxicity screening test (OECD 422)	20, 60 and 200 mg/kg bw/day by gavage	A noisy respiratory sound, which seems to be related to irritation of the respiratory tract, was observed in some females following daily oral exposures to 200 mg/kg bw of ptBP. It is proposed that this irritation is related to direct daily exposure of the respiratory tract to ptBP due to repeated administration by oral gavage. The study reported that the "Irritation of the oral cavity or the trachea caused by oral administration of the tested substance might be involved in the abnormal respiratory sounds observed in 200 mg/kg dose group in the present study." But it is recognized that "However, pathological examination was not able to support this". In this study, animals were dosed by "oral gavage" suspended at 4% concentration in a 5% methylcellulose suspension in water. One female animal died and this was considered to be due to "an administration mistake" in which "gross necropsy showed sub involution and change in colour (red or black) in the lungs" and "histopathological examinations	MHW, Japan, 1996

				revealed congestion in lungs".	
Rats Sprague Dawley rats	F0: 28/sex/ group F1: 24 sex/ group	Two generation reproduction study	diet of 0, 800, 2500 and 7500 ppm available continuously.. The average doses: 70, 200, 600 mg/kg bw/day.	In some periods, at initiation of the F0 and F1 generations, in the group of high dose, the actual intakes were higher than 700 and 1300 mg/kg/day for males and females, respectively. ptBP intakes over 1300 and 1700 mg/kg/day were observed during the second and third weeks of lactation for F0 and F1 females, respectively. No observations of respiratory noise and respiratory irritation were indicated.	

5.10.2 Summary and discussion of respiratory tract irritation

The background information is based on:

- Acute inhalation (Klonne *et al.* 1988)
  - Exposure to static saturated vapor for 6 h
  - Limit test at dynamically generated dust aerosol (5600 mg/m3) for 4 hour
- Repeated dose toxicity:
  - Combined repeated dose toxicity and reproductive/developmental toxicity screening test (OECD 422) (MHW, Japan, 1996)
  - Other data (Two generation reproduction toxicity study)

Inhalation studies in humans

No studies examining acute inhalation toxicity of p-tert-butylphenol in humans were found. Occupational biomonitoring of urine metabolites has been described in several studies (described in the RAR) and urine metabolites has been detected and identified. In one study, average exposure was estimated to be 0.39 mg/m3 (n=15) in one group and 0.10 mg/m3 (n = 5) in another group. The urine excreted mean urine concentration of p-tert-butylphenol was 5.07 µg/ml and 3.03 µg/ml.

Conclusion: Exposure by inhalation in human has been demonstrated by detecting and identifying metabolites in urine but no data about respiratory effects are described in these studies.

Acute inhalation study in animals

No acute inhalation toxicity study fulfilling current test guidelines is available. However, a non-guideline acute inhalation study is published (described in Klonne *et al.*, 1988). This paper includes several studies that have also been considered for dermal and eye irritation. Two inhalation experiments are described in the paper:

Exposure to saturated vapour for 6 h

Rats were exposed in a static generated vapour. It was prepared putting 100g of the substance and leaving it to statically saturate the chamber. The actual concentration in the air of the chamber is not indicated. We can assume it to be around the concentration determined by its relative vapour pressure (0.5 Pa at 20 °C) in the air close to the site of deposit of the substance and somewhat lower in the whole chamber. No effects were observed in the rat exposed for 6 hours in this chamber. There were no effects on body weight and no signs of toxicity following clinical observation and necropsy. No respiratory effects are indicated.

Another similar study is mentioned in the RAR with an 8 h exposure period (BASF 1971) with no observed effects. No details on this study are indicated.

A limit test at dynamically generated dust aerosol (5600 mg/m3) for 4 hours

Five male and five female rats (Sprague-Dawley) were exposed in a 120 liter chamber for 4 hours to p-tert-butylphenol as **dust aerosol** of 5600 mg/m3 (median particle diameter of 3.6 µm) with additional vapour component of 30 mg/m3. Dust aerosol was generated by leading vapour from melted p-tert-butylphenol (110 °C) to the exposure chamber where the vapour condensed in air to **fine powder**.

Clinical signs observed on the day of exposure and up to 7 days post exposure included signs of mucosal irritation (perinasal, perioral, and periocular encrustation) and signs of respiratory distress (audible respiration, gasping, and a decreased respiration rate). It is unclear if the mucosal irritation is cased by the "dust" particles or by the substance as animals were exposed to fine powder suspended in the air. No further details on severity of clinical signs of toxicity or number of animals affected are given in the report. Within one to two days following exposure, one rat of each sex died. The dead animals showed dark red or purple discoloration. This study demonstrates irritating properties of p-tert-butylphenol when administered as dust aerosol. It is unclear if this is due to the dust of or specific effect of the substance. The high dose of 5600 mg/m3 is over the cut off of 5000 mg/m3 indicated in the guide for STOT single exposure by inhalation for dust aerosols as STOT SE 2. Therefore there are objective criteria for this to be considered a high dose.

Repeated dose study

A Combined Repeated Dose and Reproductive Toxicity Screening test (OECD Test Guideline 422; MHW, Japan 1996)

Sprague-Dawley rats were dosed by **oral gavage ("oral intubation")**. Specific details of the technical procedure are not described in the available unofficial translation of the report (i.e: flexible tubing or rigid feeding needles, animal immobilization, rate of liquid administration …)

The test substance, p-tert-butylphenol [CAS No.; 98-54-4, Purity; 99.9 % (wt %)] is a white flaky substance that is stable at room temperature. A 4 % suspension (for 200 mg/kg dose group) was prepared in 0.5 % methylcellulose solution in water (1500cp, Wako Junyaku Co., Lot No.: DSG 1980; Japanese Pharmacopoeia; San-a Seiyaku Co., Manufacture No.: DH004)]. The suspension was diluted gradually for the other doses. It was shown that the suspension was stable at room temperature for eight days, under dark light conditions. The suspension was used within seven days.

A preliminary range finding study (5 rats/sex/group) was carried out in order to determine the doses of p-tert-butylphenol for the main test. Five male and female eight-week old Sprague-Dawley rats per dose group were **administered by oral gavage ("oral intubation")** p-tert-butylphenol at daily doses of 0, 250, 500 and 1000 mg/kg for two weeks, after which they were weighed and examined for toxic effects. At 1000 mg/kg, two females and one male died. Decreases in weight gain and abnormal respiratory sounds accompanying difficult breathing were observed in three females. At 500 mg/kg, the number of animals with abnormal respiratory sounds, the same type as at 1000 mg/kg, increased gradually during the treatment period, and at the end of treatment these symptoms were observed in three males and three females. Based on these results, daily doses of 500 and 1000 mg/kg were considered to exceed the maximum tolerable dose. At 250 mg/kg, no significant effect on weight gain was observed. However, abnormal respiratory sounds were observed in one female. Considering that the number of animals with abnormal respiratory sounds increased progressively during treatment with 500 and 1000 mg/kg of p-tert-butylphenol and that the treatment period of the main study would be longer than the preliminary study, 250 mg/kg was also considered to slightly exceed the maximum tolerance dose. Thus, it was decided to use 200 mg/kg/day for the high dose, and 60 and 20 mg/kg/day for middle and low dose, respectively.

In the main study, 13 rats/sex/group were dosed by oral gavage with 0, 20, 60, 200 mg/kg bw/day. Approximately 4 weeks of exposure in males, and from 14 days before mating to day 3 of lactation in females. At 200 mg/kg bw/day, one female was found dead on day 43;

however, this was considered to be caused by an administration mistake. Some females of the highest dose group showed stridor, associated with dyspnea (abnormal respiration). Further, in the F0 generation at 200 mg/kg some females showed abnormal respiratory sound after the 3rd administration and a total of four animals showed abnormal respiratory sound at the end of the experiment.

The respiratory stress observed was considered to be caused by irritation of the respiratory tract during administration. However, **histopathological examinations did not reveal signs of irritation of the respiratory tract**. The mean plasma concentration of albumin in the males was slightly lower in the 60 and 200 mg/kg dose groups (6 % and 13 %), accompanied by decrease in plasma protein in the 200 mg/kg bw/day males (6 %). A significant lower mean red blood cell count (5 %), and higher mean white blood cell count (38 %) in males in the 200 mg/kg bw/day dose group was also reported. No compound related morphological changes were observed during pathological examination of parental animals. In males there was a slight (less than 5 %) increase in mean relative liver weight. Based on respiratory distress in exposed females and effects on several blood parameters in males, the NOAEL in parental animals is considered to be 60 mg/kg bw/day. Admittedly, the severity of the systemic toxicity observed is questionable.

However this is not confirmed by actual observations of irritation as histopathological examinations did not reveal signs of irritation of the respiratory tract. In the available report of the original study (unofficial translation) it is stated that *"Irritation of the oral cavity or the trachea caused by oral administration of the tested substance **might be** involved in the abnormal respiratory sounds observed in 200 mg/kg dose group in the present study."* In fact, another study showed abnormal respiratory sounds in rats caused by chemical substance that is irritating, and it is recognised that ***"However, pathological examination was not able to support this"***. In this study, animals were dosed by "oral gavage" suspended at 4% concentration in a 5% methylcellulose suspension in water.

Oral gavage is an exposure way that is not expected to occur in humans and how the "physical" manipulation of the procedure has been contributing to the respiratory problems observed is unclear. The substance is suspended at 4% concentration in a 5% methylcellulose solution in water and administered into the stomach by gavage and so probably using a tube-needle from the mouth to the stomach. The concentrated preparation and also the needle may hence be in direct contact with the upper respiratory tract. In fact, one female animal died and this was considered to be due to "an administration mistake" in which "gross necropsy showed sub involution and change in colour (red or black) in the lungs" and "histopathological examinations revealed congestion in lungs".

Another available study for oral repeated exposure is the following:

> Two generation reproduction study, OECD Test Guideline 416, US EPA Guideline OPPTS 870.3800 (Clubb and Jardine, 2006). Sprague Dawley rats (F0: 28/sex/group, F1: 24 sex/group, oral exposure in the diet)

In the *two generation reproduction study*, p-tert-butylphenol was administered orally, by a mixture with the diet at concentration of 0, 800, 2500 and 7500 ppm. The diet contained a constant concentration of test item and was available continuously to the animals. The average doses estimated from the food consumption were 70, 200, 600 mg/kg bw/day. In some periods, at initiation of the F0 and F1 generations, in the group of high dose, the actual intakes were higher than 700 and 1300 mg/kg/day for males and females, respectively. p-tert-butylphenol intakes over 1300 and 1700 mg/kg/day were observed during the second and third weeks of lactation for F0 and F1 females, respectively. No observations of respiratory noise and respiratory irritation were indicated.

Human data
No human data are available on respiratory effect of p-tert-butylphenol

Based on the noisy respiratory sound observed in the Combined repeated dose toxicity study (OECD 422) and the respiratory effects observed in the rat acute inhalation study (limit test), p-tert-butylphenol was proposed to be regarded as severely irritating to the respiratory system and classification according to CLP criteria with STOT SE 3 - H335 was proposed by the dossier submitter. This was also *agreed at TC C&L in March 2006 (Xi; R37 according to Directive 67/548/EEC).*

However there are arguments for no classification as follows:

The data of the respiratory noise observed in the combined oral repeated dose toxicity study have uncertainties and the value of it for classification is questioned by RAC. The study was done by oral gavage which is a non-expected way of exposure in humans and this might have caused dust to enter the respiratory tract. Moreover the physical manipulation of the daily intubation may cause additional physical/mechanical effects. In fact, one female animal died and this was considered to be due to "an administration mistake" in which "gross necropsy showed sub involution and change in colour (red or black) in the lungs". The effect is not confirmed by the histopathological examination and it is not confirmed in the two generation study at higher doses by oral intake in the food.

In the limit test with inhalation exposure (described in Klonne *et al.*, 1988), animals were exposed to dust aerosol ("fine powder"). It can not be excluded that the irritating effect could be an unspecific consequence of the inhalation of particles rather than a specific effect of the test substance, but after evaluating the data recognizing also the irritating effects on skin and eyes, it is considered by RAC that the respiratory effects are most likely caused by the substance itself. The dose at which the effects were seen is however very high (5600 mg/m3). For STOT SE 3, there is no cut-off value for classification indicated neither in the CLP Regulation, nor in the CLP guidance since the classification is primarily based on human data. It can however be compared with the cut-off values used for classification as STOT SE 2 for inhalation by dust aerosols of 5 mg/l/4h (correlating to 5000 mg/m3). The dose at which effects were seen is hence higher than this cut-off value.

Taken together, there are therefore some doubts whether the data available provide enough evidence for classification for respiratory tract irritation under CLP.

In the criteria for STOT SE 3 – H335 in the CLP Regulation it is stated that the classification is mainly based **on human data**, but it is also stated that animal data may be used as supportive in a weight of evidence evaluation. There are no human data for supporting the classification. However RAC considers that from a scientific point of view the lack of human data is secondary for the justification for no classification.

The animal data in the repeated dose study do not provide clear evidences for supporting the classification for this hazard class due to the uncertainty in the way of dosage by gavage and histopathology data not supporting it. The data of acute respiratory studies showed some respiratory effect when exposed to high concentration of dust aerosol but the concentration is considered too high to be relevant. No effects are indicated in two studies in saturated atmosphere of p-tert-butylphenol. Therefore, although general irritating properties of p-tert-butylphenol were demonstrated (see skin irritation and eye damage) the experimental data in repeated dose toxicity and respiratory exposure does not support classification for specific target organ toxicity.

Comparison with criteria:

Criteria for Category 3 for respiratory tract irritation	**Data fulfilling the criteria**
(a) respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain,	No human data is available. Respiratory noise observed in the Combined repeated dose

choking, and breathing difficulties are included. **This evaluation will be based primarily on human data**;	study by oral gavages. There are doubts about how careful the oral intubation was done as one animal died due to a mistake in the intubation. Effects in mucosa were not confirmed by the histopathological examination and it is not confirmed in the two generation study at higher doses by oral intake in the food.
(b) **subjective human observations** could be supported by objective measurements of clear respiratory tract irritation (RTI) (such as electrophysiological responses, biomarkers of inflammation in nasal or broncho alveolar lavage fluids);	No human data is available.
(c) **the symptoms observed in humans** shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. **Ambiguous reports simply of 'irritation' shall be excluded** as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory irritation; d) there are currently no validated animal tests that deal specifically with RTI, however, useful information may be **obtained from the single and repeated inhalation toxicity tests.** For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. **Such animal studies can be used as part of weight of evidence evaluation**; (e) this special classification would occur only when more severe organ effects including in the respiratory system are not observed.	No human data is available. No specific unequivocally irritation data are described in repeated dose toxicity study. Noisy respiration is indicated. Dosing by gavage might have produced physico-mechanical disturbances. Histopathology examination is not supporting specific tract irritation. No repeated inhalation study available. A limit test, exposure via inhalation at a dose of 5600 mg/m3 and a vapour component showed signs of mucosal irritation and respiratory distress. The concentration is however considered high, (higher than for example 5000 mg/m3 used as cut off for STOT SE 2).

Conclusion:

Based on the available data, no classification for STOT SE 3 – H335 is proposed.

5.11 Other effects

Human data

Occupational exposure

The main routes of exposure for workers are expected to be by inhalation and dermal contact. Ingestion is not considered to be relevant for occupational exposure. Exposure may take place during production of ptBP, when ptBP are used as a chemical intermediate or when resins and paints are used by professionals. PtBP will be handled and used both in molten and solid form and workers might be exposed to vapour, liquid or dust. The highest exposure levels are expected when performing processes at high temperatures, when handling dust or when resins are manually handled or used in working operations creating aerosols.

General population

Potential consumer exposure is via direct use of products with phenolic resins or epoxy resins containing residual ptBP monomers, or via use of the final product containing residual concentration of ptBP. Consumers may also be exposed to ptBP in drinking water from drinking water reservoirs or pipelines. The main exposure from final products is expected to be from adhesives used in leather products such as shoes, and from cosmetics. Some exposure may also occur from various consumer articles such as eyeglass frames, tooth and hair brushes, hearing aids, however, exposure from these products are considered to be low. The main routes of exposure to consumer products are by dermal contact (e.g. glued leather products) and by ingestion of food products into which ptBP have migrated from the food/water container or packaging (e.g. food contact applications). For humans exposed indirectly from the environment, the main exposure is expected to be from ingestion. (Norwegian Product Register (2003)).

5.12 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

No classification required.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Environmental classification of p-tert-butylphenol was discussed and in September 2005 the environment working Group agreed N; R 51/53. However as the criteria for environmental classification are changed in CLP, the criteria are no longer fulfilled and environmental classification is therefore not presented in this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

p-tert-butylphenol was on the 4th priority list of the Existing Substances Regulation and its classification was reviewed in the context of the Risk Assessment procedure as it was a requirement to harmonise classification for all endpoints. We have included all endpoints concluded by TC&CL despite the fact that they do not only cover the CMR hazard classes and respiratory sensitization.

The classification of p-tert-butylphenol was discussed at ECB by the TC C&L in September 2005, March 2006 and September 2007.

Environmental classification of p-tert-butylphenol was discussed and in September 2005 the environmental working group agreed to classify ptBP with N; R 51/53. However as the criteria for environmental classification is changed in CLP, the criteria are no longer fulfilled and environmental classification is therefore not presented in this dossier.

See Annex I of this report (Follow-up III of the meeting of the Technical Committee on Classification and Labelling in Arona, 26-28 September 2007) for the conclusion of the TC C&L group.

See Annex II of this report for the discussion of ptBP in the TC C&L group in March 2006 and October 2006.

See Annex III of this report (Follow-up III of the meeting on environmental effects of existing chemicals, pesticides & new chemicals in Ispra, 28-30 September 2005) for the discussion of ptBP in the TC C&L group.

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ANNEX I

FOLLOW-UP III OF THE MEETING OF THE TECHNICAL COMMITTEE ON CLASSIFICATION AND LABELLING IN ARONA, 26-28 SEPTEMBER 2007

I025 (N) **4-tert-butylphenol** **Not listed in Annex I** **CAS No: 98-54-4** **EC No: 202-679-0**	*March 2006:* <u>Reproductive toxicity</u> **N** had made a classification proposal including classification for both endpoints for reproductive toxicity, Repr. Cat. 3; R62-63 (ECBI/16/06 Add. 1). The discussion was postponed as a 2-generation study had not yet been evaluated by the TC NES.
<u>Classification:</u> Repr. Cat. 3; R62 *Agreed 0907* Xi; R37/38 – R41 *Agreed 0306* N ; R51-53 *Agreed 0905* **<u>Labelling:</u>** Xn R: 37/38-41-62-51/53 S: (2-)26-36/37-39-61	**IND** had provided the TC C&L with a summary of the 2 generation study (ECBI/16/06 Add. 4) distributed with FU III of the March 2006 meeting. *In October 2006* the TC C&L agreed provisionally not to classify the substance as R63 (development) and to classify the substance as R62 (fertility). A lot of questions arose regarding the 2-generation study (Clubb and Jardine, 2006) on which the Norwegian proposal for the application of R62-63 was based and for which a summary had been made available to the TC C&L. The relevant part of the RAR, where the study by Clubb and Jardine, 2006 is described has been submitted by **N** (ECBI/16/06 Add. 5).
<u>Classification assigned in accordance with the CLP Regulation:</u> Repr. 2; H361f STOT Single 3; H335 Skin Irrit. 2; H315 Eye Dam. 1; H318 Aquatic Chronic 2; H411	*MS experts were asked to respond during the written procedure if the provisional agreement of the October 2006 meeting could be confirmed.* **S and NL** agreed to the provisionally agreed classification proposal for reprotoxicity i.e. Repr. Cat. 3; R62. **IND** sent a review on reprotoxicity of 4-tert-butylphenol for consideration at the September meeting in document ECBI/16/06 Add. 6 (MS only), supporting no classification for both fertility and developmental effects.

	UK would like to discuss the reprotoxicity of 4-tert-butylphenol on basis of the review distributed by Industry. **F** support the provisional classification agreed at the October 2006 meeting: - Category 3 for fertility because of the decrease in ovary weight and the atrophy of vaginal epithelium in the high-dose group in the both generations and in the mid-dose group in the first generation. It was accompanied by a slight reduction in implantation sites in the high-dose groups that is not within the historical control incidence in the F1 females. Besides, the decrease of ovary weight in the high-dose F1 females was more severe (-28%) than the general decrease of body weight (-17% during pre-mating and -13% during the lactation period) and it can not be attributed to a secondary effect. - No classification for development because the effect seen on pups survival at the first generation were not reproduced at the second generation. **BE:** After examination of the documents received from N and a detailed analysis of the effects, BE would like to have a verbal discussion concerning this substance at the next meeting for the fertility classification. On basis of the new document by IND and the response from UK and BE, it was decided to discuss reprotoxicity of 4-tert-butylphenol at the September 2007 meeting. *MS were invited to send further comments/positions within the deadlines for the September meeting to facilitate the discussions.* No further comments received. ***In September 2007*** the TC C&L agreed to confirm the provisional classification for Repr. Cat. 3; R62 (Repr. 2 H361f) from the last meeting, and they also confirmed that it would not be necessary to classify for developmental effects. ⇨ **Next ATP**

ANNEX II

DISCUSSION OF PTBP IN THE TC C&L GROUP IN MARCH 2006 AND OCTOBER 2006

TC C&L meeting March 2006:

4-tert-butylphenol (I025)

(CAS number 98-54-4, EC number 202-679-0)

Currently not classified in Annex I

Classification proposal Xi; R37/38 – Xi; R 41, R43, Repr Cat 3; R 62-63, N; R 51/53

ECBI/16/06 Adds 1 - 3

In **September 2005** the environment working Group agreed N; R 51/53.

Norway introduced the proposed classification of this substance. They drew attention to the fact that eye effects showed persistence warranting the application of R 41. For skin sensitisation there were some variable responses but sufficient case studies existed to justify R 43. Norway also indicated their support for a French proposal to replace R 38 by R 34.

Skin and eye irritation

Germany suggested it that there was no full skin necrosis within 4 hours and that R 38, and not R34, was appropriate. This position was supported by Industry, UK, Finland and Belgium. The discussion concluded with agreement that the substance should be classified with Xi; R 37/38 - R 41.

Skin sensitisation

Industry opposed classification for this end point. It was reported that the data was derived from an old test protocol with a significant risk of misdiagnosis. Other studies to modern protocols and standards showed no effect. After some discussion the Group agreed provisionally not to assign R 43 although Norway was invited to provide additional information during the follow-up period.

Reproductive toxicity

The United Kingdom suggested that classification for fertility with R62 was borderline as the effects seen were within the historical range. However France indicated that they wished to classify for this effect. The Chair said that it was not possible to reach a conclusion on this endpoint and it would need to be discussed again. She asked for more information, particularly on the controls. On developmental toxicity industry reported that effects had only been seen where there was marked maternal toxicity. After some discussion the Chair said that further consideration of this endpoint would be needed at the next meeting.

Conclusion:

TC C&L agreed to Xi; R 37/38 - R 41. Reproductive toxicity should be discussed at the next meeting. The discussion was postponed as a 2-generation study had not yet been evaluated by the TC NES.

Follow-up:

IND has provided the TC C&L with a summary of the 2 generation study (ECBI/16/06 Add. 4) distributed with the last Follow-up sheet.

TC C&L October 2006:

4-tert-butylphenol (I025)

(CAS number: 98-54-4, EC number: 202-679-0)

Currently not classified in Annex I

Classification proposal Xi; R37/38 – Xi; R 41, R43, Repr Cat 3; R 62-63, N; R 51/53

ECBI/16/06 Adds 1 - 3

In **September 2005** the environment working Group agreed N; R 51/53.

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Conclusion:

TC C&L agreed to Xi; R 37/38 - R 41. Reproductive toxicity should be discussed at the next meeting. The discussion was postponed as a 2-generation study had not yet been evaluated by the TC NES.

Follow-up:

IND has provided the TC C&L with a summary of the 2 generation study (ECBI/16/06 Add. 4) distributed with the last Follow-up sheet.

New documents:

ECBI/16/04 Add. 4, A summary of the Clubb and Jardine, 2006 study

ECB reported that reprotoxicity was the open issue both development and fertility. The report from a 2-generation study (Clubb and Jardine, 2006) was awaited. A summary had already been available at the last meeting. In the RAR this study had been integrated and evaluated already by the TCNES that did not comment the revised reprotox part of the RAR which meant that they agreed to it.

D referring to the new study asked Norway for some clarifications. In the F1 generation a reduction in brain weight was found indicating severe maternal toxicity. Apparently there was no effect on sperm number. D asked also whether other effects were observed adding that IND had mentioned that the weight reduction observed was within the historical control. **N** answered that that the main effects in the study were observed in the females, so no further details were given on effects on the testis. Histopathological investigations were not carried out. Effects on implantation were observed and they were most severe in the F1 generation.

IND agreed that the table given in their document (ECBI/16/04 Add. 4, A summary of the Clubb and Jardine, 2006 study) was maybe not clear enough. It was difficult to compare directly the bodyweights of the F1 generation with the background data which are in the range of the historical control. **UK** judged the effects on fertility to be borderline. They proposed neither to classify for fertility- nor for developmental effects.

B noted that maternal toxicity was seen already at the medium dose and moreover the figures of the implantations were well within the historical controls. That meant no classification both for development and fertility. **NL** favoured classification based on effects on fertility since there was indeed a reduction in ovary weight while no classification was necessary for development. **S** agreed with Norway in regard to the fact that the fertility effects were seen in females (F0 and F 1 females) adding that also a classification for development was warranted. **B** noted that indeed the ovary weights were reduced but pointed out that that was an unspecific effect and added that it was not normal that brain weight (F1 females) was reduced at the same time. That was a clear sign of maternal toxicity. **D** thought that was a borderline case asking whether there were dead pups as well. He added that during lactation enhanced pup mortality but also reduction in litter weight was seen (F1 generation). **F** supported classification as Cat. 3 for fertility but not a classification for development since the effects occurred in parallel to and were obviously due to maternal toxicity. **UK** added that they could agree with Cat. 3 for fertility on the basis of indirect effects. However if only direct effects on fertility would be considered no classification would be warranted.

IND drawing the attention to the reduced body weight gain of pups and the reduced implantations seen added that that was directly related to the reduced body weight gain of the animals. Data showed that restriction of calorie intake without exposure to substances could lead to reduced implantations. The effects seen were clearly related to reduced food uptake and not directly substance induced.

In order to come to a decision **the Chairman** suggested to first distribute the extended version of the study from Clubb and Jardine 2006 as laid down in the RAR also to the TC C&L since they had seen only summaries form Norway and IND. Then a final recommendation should be taken. N agreed to submit an extended study description in the follow-up. After receiving consent from the TC C&L **the Chairman** concluded that it was provisionally agreed not to classify the substance for development and to provisionally classify it as Cat. 3 R 62 for fertility. A final recommendation, however, should be made by MS after looking at the extended study report from N either in the follow-up of this meeting or at the next meeting.

Conclusion:

The TC C&L agreed provisionally not to classify the substance as R63 (development) and to classify the substance as R62 (fertility). A lot of questions arose regarding the 2-generation study (Clubb and Jardine, 2006) on which the Norwegian proposal for the application of R62-63 was based and for which a summary had been made available to the TC C&L. N was asked to submit the relevant part of the RAR where the study is described in detail prior 1 December.

Follow up: Norway has submitted the extended study report (ECBI/16/06 Add. 5) in follow-up II. Therefore the substance can be concluded either in the written procedure prior to or discussed at the TC C&L meeting March 2007.

ANNEX III

FOLLOW-UP III OF THE MEETING ON ENVIRONMENTAL EFFECTS OF EXISTING CHEMICALS, PESTICIDES & NEW CHEMICALS IN ISPRA, 28-30 SEPTEMBER 2005

4-Tert butyl phenol; 4-(1,1-Dimethyl -ethyl) phenol (NO) Not in Annex I

CAS: 98-54-4 EC: 202-679-0 HH: to be discussed.

Classification S -phrases	Toxicity	Degradation	Bioaccumulation	Escape clause
N, R51-53 **S61**	1 < L(E)C_{50} ≤ 10	Readily degradable (based on data)	log K_{ow} > 3 BCF >100	Not relevant.
Specific concentration limits:				

IND has submitted document ECBI/20/05 Add. 1 on the substance in time for the meeting. However, ECB failed to post the document on the agenda. It was then distributed as a room document and then again in FU I. MS are invited to react to the document in the FU period.

FU II: NO has sent in the relevant part of the RAR (ECBI/20/05 Add. 2).

FU III: Sweden has reacted to document ECBI/20/05 Add.1. Sweden, referring to the bioaccumulation of ptBP noted that IND in its letter questioned the use of the Freitag et al. 1984 study in determination of the BCF of the substance. Sweden believed that the question of bioaccumulation had been thoroughly discussed by the TC NES and the value of BCF (i.e. 120) had been accepted and therefore they did see no reason for rejecting the study for classification purposes.

The substance will be classified as outlined in the box.