CLH report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: p-tert-butylphenol

EC Number: 202-679-0

CAS Number: 98-54-4

Submitted by Norway

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

In March 2006 TC C&L agreed to Xi; R 37/38 - R 41. In September 2007 TC C&L agreed to Rep. Cat.3; R62.

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 is changed in CLP, the criteria is no longer fulfilled and **e**nvironmental classification is therefore not presented in this dossier.

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

Xi: R37/38 R41,

Repr. Cat 3; R62

Not classified for the environment

Proposed classification based on GHS criteria:

STOT SE 3; H335

Skin irrit. 2; H315

Eye dam. 1; H318

Repr 2; H361f

Not classified for the environment

Proposed labelling:

Xi; R37/38, R41

Repr. Cat 3; R62

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

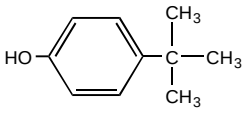
Chemical Name: p-tert-butylphenol

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		
VII, 7.11	Explosive properties	3.14		
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15		
VII, 7.14	Granulometry	3.5		
XI, 7.15	Stability in organic solvents and identity of relevant	3.17		

	degradation products			
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-t-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 N; R 51/53. However as the criteria for environmental classification are changed in CLP, the criteria is no longer fulfilled and **e**nvironmental 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 Chemical Company (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		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	Klonne et

rats			placed for 18 hours prior to the introduction of the animals.	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). 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.

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

5.3 Irritation

5.3.1 Skin

Table 5: Irritation, skin

Species	No. of animals	Exposure	Conc.	Dressing: occlusive semi-occlusive open	Observations and remarks	Ref.
New Zealand Rabbits	1 male2 females	4 hours	500 mg moisted with distilled	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,	Sandoz Chemicals, 1991

			water		24, 48 and 72 hours, and 7 and 14 days after dosing. The material produced severe erythema and very slight to moderate oedema. Mean scores erythema: 24 hours, score 4; 72 hours, score 3.4; 14 days, score 0. Mean scores oedema: 24 hours, score 2; 72 hours, score 1.7; 14 days, score 0. Other adverse skin reactions noted were small areas of white-coloured necrosis (all exposed skin sites at 24 and 48 hours), well-defined erythema surrounding scabs, hardened light brown-coloured scab, thickening of the skin, crust formation and reduced re-growth of fur. No irreversible skin alterations were reported after 14d and the substance was 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 male3 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 male3 females	4 hours	500 mg	Abraded 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 males1 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	Schenectady., 1982

					patch and approximately 48 hours thereafter. Mean scores: Erythema: 4 hours, score 2; 48 hours, score 2.3. Oedema: 4 hours, score 1.5; 48 hours, score 1.7. One male showed necrosis at 48 hours. No further details are provided. The primary irritation index was found to be 3.4 on a scale to 8. This study supports the indications that ptBP can be severely irritating and also corrosive to skin.	
Rabbits	3 male3 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 male5 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, whereas desquamation and scabs were present at day 14.	Klonne et al., 1988/ UCC 1985
Black Guinea pigs	5 male5 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 animals	Exposure	Conc)	Observations and remarks (specify the experimental conditions, score and evaluation method)	Ref.
Rabbits	6 animals	24 hours	80 mg of finaly 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 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.	Shell, 1980
				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 Respiratory tract

Table 7: Irritation, respiratory tract

Species	No. of animals animals	Exposure	Conc.	Observations and remarks	Ref.
Sprague-Dawley rats	5 male 5 female	4 hours	5600 mg/m^3	Respiratory toxicity was observed in the rat acute inhalation study (limit test). Mucosal irritation (perinasal, perioral, and periocular encrustation) and respiratory distress (audible respiration, gasping, and a deceased respiration rate) were observed following exposure to ptBP. The animals were exposed in an animal chamber to ptBP in the form of dust aerosol (of 5600 mg/m^3) with an additional vapour component of 30 mg/m^3.	Klonne et al., 1988

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.	MHW, Japan, 1996

5.3.4 Summary and discussion of irritation

*Skin irritation***:**

Corrosive effects have been reported. In the most recent study conducted according to accepted guidelines ptBP was found to be highly irritating to skin. In this study small area of white-coloured necrosis was induced, but these lesions were not regarded as a corrosive effect according to EU directive 67/548/EEC and CLP . As no further information on the nature of the white coloured necrosis is provided, we have considered that ptBP is not corrosive. Two studies have reported the occurrence of skin necrosis in a minority of exposed animals following a 4-hour exposure (Klonne et al., 1988/UCC 1985; Schenectady, 1982). After prolonged skin contact (24 hours) in a dermal, acute toxicity study (Klonne 1988/UCC 1985) necrosis was reported in all exposed animals. From the available data it seems that in most animals (rabbits) mild to severely irritation is observed, whereas in a minority corrosivity is reported. Only limited information related to the nature of the corrosivity and necrosis reported is available. Prolonged exposure to high doses of ptBP induces persistent necrosis in all exposed animals.

Based on the animal data available a classification according to CLP criteria with Skin irrit. 2; H315 is proposed.

Classification Xi: R38 (CLP Skin irrit. 2; H315) was agreed at TC C&L in March 2006.

Eye irritation:

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

Based on the above information ptBP is regarded as severely irritating to eyes and a classification according to CLP criteria with Eye dam. 1; H318 is proposed.

Classification Xi: R41 (CLP Eye dam. 1; H318) was agreed at TC C&L in March 2006.

Respiratory irritation:

Based on the above information ptBP is regarded as severely irritating to the respiratory system and a classification according to CLP criteria with STOT SE 3; H335 is proposed.

Classification Xi: R37 (CLP STOT SE 3; H335) 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 animals5 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 animals6 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 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	Malten, 1967

			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 sensitizationhumans			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 is negative and one is positive. The negative studies use the GPMT test and have been performed according to current test guidelines and GLP. The positive study is an older study and the protocol is not well described. No firm conclusions can be drawn based on the animal studies. However, based on the scientific quality of the studies it appears more likely that ptBP does not cause skin sensitisation in animals.

ptBP has been reported to be the first allergen identified in ptBP-FR (Zimerson and Bruze in Kanerva et al.; Handbook of Occupational Dermatology, 2000). There are several sensibilisation studies performed using patch tests of patients with either work related contact allergy or general allergy. Furthermore, many case reports were found in the literature. Many of them used ptBP-FR and are of limited value in evaluating a possible sensitisation potential for ptBP. The results from these studies/reports give a very variable picture of human sensitisation to ptBP. In Contact Dermatitis of Fisher, 1986, (p. 649) it is stated that in the 1950s and 1960s an excess of free ptBP was present in the resin. Sensitisation studies indicate an allergic reaction to the resin is frequently caused by a reaction to both the resin itself (PTBPFR) and to the free PTBP. It was also recommended to eliminate the excess of free ptBP 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 ptBP and are of more importance when assessing the sensitisation potential of ptBP than studies performed later (Rudner, 1977; Romaguera et al., 1981).

In October 2006 the TC C&L agreed that the human data on ptBP on skin sensitisation 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 TC C&L Group agreed provisionally not to assign R 43.

In September 2007 the TC C&L agreed not to classify ptBP for skin sensitisation.

Respiratory sensitisation:

There is not sufficient data to draw any conclusions with respect to respiratory sensitisation.

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 toxic sign was 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 as 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 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.	MHW, Japan, 1996
Male Syrian Golden Hamsters		20 weeks	The study addressed the effects of phenolic compounds, including ptBP, on the induction of	Hirose,

(15)	1.5% ptBP in the diet (approximately 1230 mg/kg bw/day)		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.	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:

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 ptBP. 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 ptBP in the diet induced moderate effects on relative kidney and liver weights.

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 activ.	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 mutation assay (Ames test)	*S. Typhimurium*, strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 as well as *Echerichia coli* WP2, and WP2 *uvr*A	0, 125, 250, 500, 1000, 2000, and 4000 µg/plate	+/- S9 mix	No genotoxicity was reported up to 4000 µg/plate. No information regarding cytotoxicity was available. The experiments were performed in triplicate or quadruplicate.	Dean et al., 199(8)5
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,	+/- S9 mix	No increase in mutant was reported following 3-6 hour exposure, either with or without metabolic activation. Following	Honma et al., 1999

		80 µg/ml exposure 3-6 hours **Secondary test**: 0, 20, 40, 60, 80 µg/m exposure 24 hours		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).	
Chromosomal aberrations (CA)	Chinese Hamster Lung/IU cells (CHL/IU)	**- S9 (continous treatment, 24 or 48 hours)**: 0, 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.	+/- 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 observation of cytotoxicity with metabolic activation. 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).	OECD, SIDS, 2000
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	+/- 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	Kusakabe et al., 2002

		dissolved in DMSO or acetone		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 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 unpublis hed, 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., 19(9)85
Cromosomal aberrations (CA)	Cultured rat liver cell line	5% solution of ptBP		No induction of CA was reported.	Dean etal., 199(8)5

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 test	Mammalian bone marrow cells	**24 and 48 hours after i.p, injection of ptBP**: 12.5 mg/kg, 25		The test was performed according to OECD Test Guideline 474. ptBP was dissolved in 0.5 % methyl cellulose. In a preliminary range-finding experiment 5 males and 5 females were exposed to 25, 50, 100 and 200 mg/kg ptBP. All animals died at 200 mg/kg, and 3 males and 4	MHW, Japan, in progress expected in 2003

		mg/kg, 50 mg/kg		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*.	

5.7.3 Human data

No data available.

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

ptBP 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. ptBP 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. Though, this *in vivo* studies have limited value due to the absence of cytotoxicity in the target tissue or lack of information in this aspect.

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 fore stomach hyperplasia, and one pappiloma 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 fore stomach (animals treated with MNNG and ptBP and animals only treated with MNNG). In 19/20 rats treated with MNNG and ptBP pappilomas were reported (13/19 rats treated only with MNNG). In 8/20 MNNG and ptBP reated rats carsinoma "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 fore stomach.	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 rat study where only one papilloma of the fore stomach was found and the uncertain mutagenic effects, it is considered unlikely that ptBP should be a human carcinogen. However, its ability to increase the frequency of squamous cell carcinomas in the rat fore stomach following initiation with MNNG indicates that ptBP may act as a tumour promoter in rats. Whether or not it may be a promotor in humans needs to be clarified. Though ptBP apparently is not a mutagen, the underlying database is not very solid.

The data available does not indicate a carcinogenic activity for ptBP, however, the database is not sufficient to address its carcinogenic properties. 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, 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.	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 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.	MHW, Japan, 1996
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	**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	Clubb and Jardine, 2006

					(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 (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 0.107g in controls) and pituitary gland (0.011 vs 0.012g in controls) were reported following covariance analysis with the body weight as the covariate. At 2500 ppm a statistically significant decrease in the weights of the adrenal gland (0.070 vs 0.079g in controls) and ovaries (0.095 vs 0.109 g in controls) were reported in females. No changes in organ weights were reported at 2500 ppm in males and at 800 ppm in males and females. **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 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.	

5.9.2 Developmental toxicity

Table 14: Reproduction, developmental toxicity

Species	**Route**	***Dose mg/kg/day ppm **Conc. (mg/l)**	**Exposure time (h/day)**	**Exposure period: - number of gene-rations or - number of days during pregnancy**	**Observations and Remarks**	**Ref.**
Sprague Dawley rats F0: 28/sex/ group F1: 24 sex/ group	Oral in diet	0, 800, 2500 and 7500 ppm corresponding to approximately 60, 200 and 600 mg/kg/day	OECD Test Guideline 416, US EPA Guideline OPPTS 870.3800	2 generations	**F0 generation:** No treatment related clinical signs were reported. A statistically significant decrease in body weight gain was reported in F0 females at 2500 ppm (95 vs 114g in controls) and at 7500 ppm (78 vs 114g in controls). At 7500 ppm the body weight in F0 females during gestation was lower compared to controls (372 vs 441g in controls), and the body weight gain was 108 vs 138g in controls. The body weight during lactation at 7500 ppm was 321 vs 353g in controls. No statistically significant changes in body weights were reported at 800 ppm in females. At 7500 ppm food consumption was statistically significant reduced in F0 females from week 1 to week 10 of treatment, prior to mating (week 1; 13.7 vs 20.6 g/animal/day in controls, week 10; 20.0 vs 22.8 g/animal/day in controls). During gestation the food consumption at 7500 ppm in F0 females was 30.4 vs 33.0 g/animal/day in controls, and during lactation 75.8 vs 91.6 g/animals/day in controls. 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	Clubb and Jardine, 2006

					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	MHW, Japan, 1996

					irritating material (for further details see section 4.1.2 repeated and prolonged exposure).	

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 ptBP 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 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.

Based on the data from the 2-generation reproduction study in rats ptBP should be classified for fertility according to CLP criteria with Repr 2; H361f.

Classification Rep. Cat.3; R62. (CLP Repr 2; H361f) 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 ptBP 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 a 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.

There is not sufficient data to draw any conclusions with respect to developmental toxicity.

5.10 Other effects

OBSERVATIONS OF HUMANS

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 find 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)).

5.11 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 is changed in CLP, the criteria is no longer fulfilled and **e**nvironmental 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.

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

In March 2006 TC C&L agreed to Xi; R 37/38 - R 41. In September 2007 TC C&L agreed to Rep. Cat.3; R62.

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 is changed in CLP, the criteria is no longer fulfilled and **e**nvironmental 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.

OTHER INFORMATION

It is suggested to include here information on any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. The data sources (e.g registration dossiers, other published sources) used for the dossier could also be indicated here.

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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:* Reproductive toxicity **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.
Classification: Repr. Cat. 3; R62 *Agreed 0907* Xi; R37/38 – R41 *Agreed 0306* N ; R51-53 *Agreed 0905* **Labelling:** 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).
Classification assigned in accordance with the CLP Regulation: Repr. 2; H361f STOT Single 3; H335 Skin Irrit. 2; H315 Eye Dam. 1; H318	*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

Aquatic Chronic 2; H411	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&LOctober 2006:

8 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.

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Skin sensitisation

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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.

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.