Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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/A2

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Adopted

12 June 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: p-tert-butylphenol
CAS number: 98-54-4
EC number: 202-679-0

General comments

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
31/01/2011	Germany / Hans Certa / ptBP REACH Consortium / Company-Manufacturer	comments are made on behalf of the REACH consortium for p-tert.-butylphenol	Ok	NA
09/02/2011	France / MemberState	The recommendations agreed at the TC C&L regarding the classification of p-tert-butylphenol for human health are supported in absence of any new study since the TC C&L discussions and in agreement with the classification proposed in the CLH report.	Thank you for the support	The opinion of RAC for classification should be based on analysing if the available information and arguments are fitting with the criteria of current CLP Regulation and not on the decision taken in the TC C&L.

15/02/2011	Germany / Franziska Wittmann / MemberState	No InChI code is given for the reference substance p-tert-Butylphenol. The code should be added as: InChI=1S/C10H14O/c1-10(2,3)8-4-6-9(11)7-5-8/h4-7,11H,1-3H3 Within the IUCLID file the occurring impurities are not specified in detail. However, it should be taken notice of the fact that within the CLH-report some ideas about the identity of the impurities are mentioned. The proposal of Norway for harmonised classification and labelling of p-tert-butylphenol is incomplete concerning labelling. Based on the outcome of the discussions at ECB by the TC C&L (s. Annex I and II of this CLH-report) labelling of p-tert-butylphenol based on Directive 67/548/EEC is as follows: Xn R: 37/38-41-62 S: (2-)26-36/37/39 And based on Regulation (EC) No 1272/2008 (without precautionary statements) labelling is as follows: Pictograms: GHS05 GHS07 GHS08 Signal Word: Danger Hazard Statements: H361f H335 H315 H318 The data of the standard information in the CLH-dossier pursuant to Annexe VII are incomplete. Although the physicochemical properties are not relevant for the classification and labelling we recommend the use of the "data waiver" because of the plausibility in the CLH dossier (see also the Risk assessment Report "p-tert-butylphenol", final approved version).	OK OK We have included S-phrases, CLP pictograms and signal word in the CLH report and in IUCLID	All the available information is taken into consideration

18/02/2011	Ireland / Health & Safety Authority	The Irish CA is in agreement with the proposed human health classification of Xi: R37/38-41; Repr. Cat. 3 R62 (STOT SE3 H335; Skin Irrit. 2 H315; Eye dam. 1 H318; Repr. 2 H361f) as previously agreed at TC C&L meetings in 2006 and 2007.	Thank you for the support	The opinion of RAC for classification should be based 0n analysing if the available information and arguments are fitting with the criteria of current CLP Regulation and not on the decision taken in the TC C&L.
18/02/2011	Sweden / Ing-Marie Olsson / MemberState	Sweden supports the agreement, on the proposed classification and labelling for p-tert-butylphenol, as agreed earlier by the Technical Committee on Classification and Labelling (Directive 67/548/EEC) ('TC C&L'). We agree that no environmental classification is valid due to the changed criteria in the CLP. Explain why no classification according to DSD is proposed.	Thank you for the support We have included an explanation in the CLH report	

21/02/2011	UK / MemberState	We understand that this is a 'transition substance' for which the C&L was previously agreed by the TC C&L. Consequently, the comments submitted below are observations meant to ease the progress of PTBP through the new CLP harmonised classification and labelling system.	Thank you for the support	The opinion of RAC for classification should be based on analysing if the available information and arguments are fitting with the criteria of current CLP Regulation and not on the decision taken in the TC C&L.
		Page 28- justification that action is required on a community-wide basis-The guidance on preparation of CLH dossiers, under section 6.2 (substances where a harmonised C&L has been agreed by the Technical Committee on Classification and Labelling and hand-over dossier), states that '... a justification for action at the community level should be provided for classification proposals in hazard classes and/or categories other than CMR and RS, unless the substance is an active substance in PPP or BP for which no justification is needed'. Therefore, we question whether previous discussion of the substance at TC C&L is sufficient to justify action at the community level regarding the classification of non-CMR and RS endpoints.	We have included this in the CLH report	The appropriate statement is included in the Opinion with the advice of ECHA Secretariat
		Page 5- Proposed Labelling- Safety Phrases- Unlike precautionary statements, safety phrases should be included in Annex VI. Therefore, we suggest that you include the relevant safety phrases in the 'proposed labelling' section of the CLH proposal. We consider the most appropriate safety phrases, to cover the human health endpoints, to be: S(2-)-26-36/37/39-46 S2 'keep out of reach of children' S26 'In case of contact with eyes, rinse immediately with plenty of water and seek medical advice', S36 'wear suitable protective clothing', S37 'wear suitable gloves' and S39 'wear eye/face protection'	We have included S-phrases in the dossier	S-phrases were added accordingly.

21/02/2011	Denmark / Peter Hammer Sørensen / MemberState	As the classification of p-tert-butylphenol was agreed in the former TC C&L group, Denmark supports the proposed classification.	Thank you for the support	The opinion of RAC for classification should be based on analysing if the available information and arguments are fitting with the criteria of current CLP Regulation and not on the decision taken in the TC C&L.

Carcinogenicity

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
21/02/2011	UK / MemberState	We agree that those data on carcinogenicity do not support classification for this hazard class.	Thank you for the support	OK

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
21/02/2011	UK / MemberState	We agree that the available data do not support classification for this hazard class.	Thank you for the support	OK

Toxicity to reproduction

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
31/01/2011	Germany / Hans Certa / ptBP REACH Consortium / Company-Manufacturer	page 35 reproduction toxicity In the conduct of a two-generation reproduction study, an extensive number of parameters and end-points are evaluated. Where there are marked effects of treatment at the highest dose, then a greater number of changes to end-points are to be expected. However, a change is not necessarily	This has been discussed in the TC&CL group earlier. There are no new data and no new arguments.	The opinion of RAC for classification should be based on analysing if the available information and arguments are fitting with the criteria of current CLP Regulation and not on the decision taken in

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		indicative of specific classifiable fertility and developmental effects. One important point in interpretation of the data in the two-generation study is to take into consideration the range of exposures to ptBP at critical life stages as well as the averages. The average ptBP intakes calculated by the rapporteur of 0, 60, 200 and 600 mg/kg/day at 0, 800, 2500 and 7500 ppm are at the low end of the range of exposures to ptBP and do not reflect the exceptionally high levels encountered for parental females and their offspring at critical life-stages. Test material intakes are higher when animals are smaller, as they eat more diet relative to body weight and are also higher at other critical life stages, such as during lactation, since lactating females consume two to three times the feed of their non pregnant status to provide nutrition for the offspring. ptBP intakes of 727 and 1427 mg/kg/day and 739 and 1346 mg/kg/day were observed a 7500 ppm at initiation of the F0 and F1 generations for males and females, respectively. ptBP intakes of 1353 and 1788 mg/kg/day and 1525 and 1814 mg/kg/day were observed at 7500 ppm during the second and third weeks of lactation for F0 and F1 generation females, respectively. Values in excess of the 1glkg/day exceed the recommended limit dose for studies of this type and clearly indicate that animals at 7500 ppm were exposed to exceptionally high ptBP levels at certain stages. Such high intakes during early critical stage of offspring development inevitably result in lower body weight and food consumption and can elicit consequential, but not necessarily treatment-related or classifiable, effects on fertility and developmental parameters.		the TCC&L. The specific data of exposure along the time of the study has been reviewed and presented in the Rapporteur 's version of the BD and taken into consideration.. The details of the observations in the original studies are analysed and taken into consideration in the opinion.

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
		Given the observed lower food consumption at 7500 consequent to exposure to high ptBP levels at critical stages, means that the data results are directly comparable with those from published studies of food restriction alone. Data of concern for classification highlighted by the rapporteur have therefore been compared with published studies of food restriction as well as in comparison with study results. With regard to specific effects, considered by the rapporteur, to be indicative of classification, food consumption and consequentially body weight were clearly retarded from high and early exposures to ptBP at 7500 ppm and, to a lesser extent, at 2500 ppm. However, such effects are indicative of general toxicity and unrelated to effects on fertility and development. The incidences of implantation scars and, consequently, numbers of pups born, were slightly lower at 7500 ppm in both the F1 and F2 litters. The incidences were within background laboratory control range and could be regarded as co-incidental. However, since such findings are seen in published studies of feed restriction alone, they are probably related to the observed retardation at 7500 ppm during maturation and considered evidence of general rather than specific fertility or developmental toxicity. Pup survival during lactation at 7500 ppm was lower than in the control in the F0 generation but, in the F1 generation, the control group showed lower survival than at 7500 ppm. Although a reduction in pup survival might be expected given the high ptBP exposure and the potential for consequent effects on maternal care during lactation, the inconsistency between survival in each generation, in any case, precludes a direct association between pup survival and fertility or developmental toxicity.		

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
		The weight of pups at birth in all groups in both generations were unaffected by ptBP treatment, indicative of no adverse effect specific from exposure throughout pre-natal development. Retardation of pup weights became evident at 7500 ppm during early lactation, considered a consequence of toxicity from high ptBP intakes as a result of increased maternal food consumption to provide pup nutrition, and possibly elicited in pups due to higher levels of ptBP in milk.. Further pup body weight retardation was observed at 7500 ppm during lactation from PND 14, considered a likely consequence of direct toxicity to the pups from high ptBP intakes from consumption of food by the pups themselves. The retardation of pup weight at 7500 ppm at various stages during lactation was considered evidence of general rather than specific fertility or developmental toxicity. Vaginal opening and preputial separation of the F1 offspring at 7500 ppm occurred 3 and 4 days later than controls, respectively. Although the female pups at 7500 ppm acquired vaginal opening after a 3-day delay, this was at a similar body weight to the controls and the delay was considered consistent with an effect due to retardation of body weight, as also seen in published studies of food restriction, rather than a specific developmental effect. Male pups at 7500 ppm also acquired their sexual maturity marker (preputial separation) later than controls (4 days) but, unlike the females, this occurred at a lower body weight. However, the male results were also consistent with those seen in a published study of food restriction alone, and are also considered likely due to reduced body weight, rather than a specific developmental effect. In both generations, ovary weights were lower than in the control group for F0 and F1 females at 7500 ppm and differences were apparent in the number and distribution of primordial versus growing ovarian follicles and in the stage of		

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		the oestrous cycle for females at necropsy. Reduced ovarian weight is observed in published studies with food restriction alone and it is likely that the observed lower ovary weight with ptBP at 7500 is similarly due to retardation rather than a specific developmental effect. Differences in the ratio of primordial versus growing follicles have been reported in published studies of food restriction, where the delay is apparently due to reduced nutrients during early weeks after lactation, precluding maturation of the follicle type. lt is possible that the change in follicle type with ptBP at 7500 ppm is similarly due to retardation rather than a specific developmental effect. However, since fewer follicles were counted in some groups than others and given the high variance, as evidenced by the large standard deviations from the means, it could not be equivocally determined whether the proportional differences in follicle type were specifically treatment related. No specific developmental effect is assumed for the difference at 7500 ppm in the stage of oestrous cycles of females at necropsy, since an arbitrary timing for necropsy is the more likely cause of the inter-group differences Lower weights were observed after co-variate analysis for a number of general and reproductive organs of F0 and F1 generation females, but for only a limited number of organs for F0 and F1 males and for F1 and for F1 weanlings. The majority of the organ weights affected were consistent with those affected on published studies of food restriction and were considered likely due to reduced body weight, rather than a specific reproductive or developmental effects. Lower brain and higher liver co-variate weights of females at 7500 ppm conflicted with the results of food restriction studies but, even with the conflict, given that these are general organs, no potential for specific reproductive effects was assumed. Histopathological examination of specified general and		

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
		reproductive organs of parental males in both generations, did not find significant effects of treatment. In the females, however, there were unusual incidences in both generations with atrophy of vaginal epithelium at histopathological evaluation. Atrophy was only present in females examined during pro-, metand di-oestrous and not during the oestrous phase of the cycle. The incidence in F0 females was 1,2,7 and12and thatforthe F1 femaleswas 1,0,0 and 14 in the controls,800,2500 and 7500 ppm groups, respectively. Since the incidence of atrophy was dependent on the stage of the cycle, some of the inter-group differences were due to the fact that females were, co-incidentally, by virtue of the arbitrary timing of necropsy at different stages of the oestrous cycle. Although one aetiology could be speculated to be related to smaller ovaries, as seen at 7500 ppm (Secfion 6.2), producing less oestrogen for vaginal development and, in turn related to the observed lower maternal toxicity from high ptBP intake, there was no consistency between individual ovarian weights and atrophied vagina. Given the lack of alternative aetiologies, an association with ptBP treatment and an effect on vaginal atrophy cannot be discounted, but are not indicative of classification for fertility effects, since all affected females were previously pregnant and successfully reared litters. When all the effects of apparent concern for classification of ptBP treatment were analysed in detail, no particular finding was highlighted as one unequivocally meeting the classification criteria as "toxic to reproduction" Cat. 3 (Cat 2 GHS), for both fertility and developmental toxicity.		
21/02/2011	UK / MemberState	We agree that the available data do not support classification for this hazard class. Page 27- Effects on fertility- The historical controls for implantations are discussed in Annex II (minutes from the TC	We suppose you mean that you agree in the classification since you say you agree, and we have proposed a classification?	We agree that the detailed description of the discussions of TC C&L in the Background document is not needed in the main text.

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
		C&L) of the CLH proposal for PTBP. For completeness, we recommend that this data should be included in the main body of the CLH report for PTBP.	We consider not to include the discussion from the former TC C&L group in the main body of the CLH report since this has been thoroughly discussed and concluded in the TC C&L group and is attached as Annexes to the CLH report.	It may be useful to only mention that it has been discussed before, but as clarified in several RAC meetings by RAC Secretariat and the Commission, the opinion of RAC for classification should be based on analysing if the available information and arguments are fitting with the criteria of current CLP Regulation and not on the decision taken in the TCC&L.

Respiratory sensitisation

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
-	-	No comments were received for this hazard class.	-	-

Other hazards and endpoints

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
31/01/2011	Germany / Hans Certa / ptBP REACH Consortium / Company-Manufacturer	page 16 The Klonne et al. 1988 study was used as a basis for the STOT 3 proposal. In this study, two exposure regimens were applied. In the 6 hour exposure to a substantially saturated vapor at static conditions, no mortality and no clinical symptoms were observed. Upon 4hr exposure to a dynamically generated respirable dust/aerosol mixture at concentration of 5.6 mg/l dust plus 0.03mg/l vapor, 20% mortality occurred. Mucosal irritation (perinasal, perioral, and	In a weight of evidence evaluation we consider the animal tests performed by Klonne et al	The details of the observations in the original study are analysed and taken into consideration in the draft opinion.

<table>
<tr><th>Date</th><th>Country / Person / Organisation/ MSCA</th><th>Comment</th><th>Dossier submitter response to comment</th><th>RAC response to comment</th></tr>
<tr><td></td><td></td><td>periocular encrustation) and respiratory distress (audible respiration, gasping, and ad decreased respiration rate) were observed but there were no macroscopic lesions in the surviving animals.

The relevant CLP criteria are for specific target organ toxicity- single exposure give the following.

Table 3.8.2

Guidance value ranges for single-dose exposures [a]

<table>
<tr><th></th><th></th><th></th><th colspan="2">Guidance value ranges for:</th></tr>
<tr><th>Route of exposure</th><th>Units</th><th>Category 1</th><th>Category 2</th><th>Category 3</th></tr>
<tr><td>Oral (rat)</td><td>mg/kg body weight</td><td>C ≤ 300</td><td>2 000 ≥ C > 300</td><td rowspan="5">Guidance values do not apply [b]</td></tr>
<tr><td>Dermal (rat or rabbit)</td><td>mg/kg body weight</td><td>C ≤ 1 000</td><td>2 000 ≥ C > 1 000</td></tr>
<tr><td>Inhalation (rat) gas</td><td>ppmV/4h</td><td>C ≤ 2 500</td><td>20 000 ≥ C > 2 500</td></tr>
<tr><td>Inhalation (rat) vapour</td><td>mg/l/4h</td><td>C ≤ 10</td><td>20 ≥ C > 10</td></tr>
<tr><td>Inhalation (rat) dust/mist/ fume</td><td>mg/l/4h</td><td>C ≤ 1,0</td><td>5,0 ≥ C > 1,0</td></tr>
</table>

(b) Guidance values are not provided for Category 3 substances since this classification is primarily based on human data. Animal data, if available, shall be included in the weight of evidence evaluation.</td><td>and MHW (1996) sufficient for classification according to 3.8.2.2.1.</td><td></td></tr>
</table>

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
		3.8.2.2.1. Criteria for respiratory tract irritation The criteria for classifying substances as Category 3 for respiratory tract irritation are: (a) respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data; (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 bronchoalveolar lavage fluids); (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. As based on the GHS criteria, the cat. 3 STOT classification are primarily to base on human data. Specific human data for PTBP is lacking due to the prevailing stringent workplace exposure limits that will not allow to irritant atmosphere concentration under occupational settings. Although it is acknowledged that PTBP has a general irritant effect, this is not considered to represent a specific target organ toxicity to the lung and is therefore already covered by the irritant classification. This is substantiated due to the fact that the rats exposed for 6hr to a saturated concentration in air did not show any clinical symptoms and signs of irritant effects only occurred at concentrations which are much higher.		
09/02/20	France /	1.3 Physico-chemical properties, Table 1: Summary of physico- chemical	Thank you for	

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
11	Member State	properties VII, 7.1o, Flammability: 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: 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 for solids: The study does not need to be conducted for solids, because the substance has a melting point < 160°C. VII, 7.13; Oxidising properties of solids: The classification procedure needs not to be applied because the organic substance contains oxygen, which is chemically bonded only to carbon.	the information We have included this in the CLH report	OK, but this is not affecting the endpoints proposed for classification.
15/02/2011	Netherlands / RIVM Bureau REACH / National Authority	On page 38 (chapter 7) It is stated that "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 environmental classification is therefore not presented in this dossier." It is however be useful to present the available hazard and fate informatione to specify which criteria are no longer fulfilled. Furthermore we also would like to note that the 2nd ATP to the CLP will be published in the foreseeable future. The 2nd ATP will come into force on the 1st of December 2012. The harmonised classification for p-tert-butylphenol will not be mandatory before the 1st of December 2012..	We have included classification for the environment in the CLH report according to 2ATP to CLP.	In the RAC-16 meeting it was clarified that the environmental issues cannot be considered in this RAC opinion. A new proposal may be submitted by an MSCA.

Date	Country / Person / Organisation/ MSCA	Comment	Dossier submitter response to comment	RAC response to comment
		The 2nd ATP will implement the 3rd revised edition of GHS in which classification can also be based on chronic aquatic toxicity. As p-tert-butylphenol is known to be an endocrine disruptor with NOEC values < 1 mg/l, it is useful to include the chronic data and use the all classification criteria including those of the 2nd ATP to the CLP.		
18/02/2011	Sweden / Ing-Marie Olsson / MemberState	Page 12- Skin irritation- We support the proposal to classify PTBP as Skin Irrit. 2 (H315) and Xi:R38 according to CLP and DSD criteria, respectively. Page 15- Eye irritation - We agree that PTBP meets the criteria for classification as Eye Dam. 1 (H318) and Xi:R41 according to CLP and DSD, respectively. Page 15- Respiratory tract irritation - We support the proposal to classify PTBP as STOT-SE 3 (H335) and Xi:R37 according to CLP and DSD, respectively. Page 38 – Environmental Hazard Assessment - We agree with the proposal of Not classified for the Environment. We do have one observation: Although we appreciate this is not part of the present dossier, we note that chronic aquatic data from the previous ESR assessment suggest a need to classify the substance as Chronic 3 when the 2nd ATP comes into force. We highlight this point for industry to consider these data at that time.	Thank you for the support We have included classification for the environment in the CLH report according to 2ATP to CLP.	In the RAC-16 meeting it was clarified that the environmental issues cannot be considered in this RAC opinion. A new proposal may be submitted by an MSCA. The proposal for respiratory tract irritation was not supported by RAC (see opinion).