Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

4-tert-butylbenzoic acid

ECHA/RAC/CLH-O-0000001579-64-01/F

Adopted

21 February 2011

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT COMMUNITY LEVEL

In accordance with Article 37(4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Name: ***4-tert-butylbenzoic acid***

EC Number: ***202-696-3***

CAS Number: ***98-73-7***

The proposal was submitted by ***Germany***
and received by RAC on ***09 July 2010***

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC (criteria)
Current entry in Annex VI CLP Regulation	none	none
Current proposal for consideration by RAC	Repr. 1B - H360F STOT RE-1 - H372 Acute Tox. 4 - H302 Note H	Repr. Cat. 2; R60 T; R48/23/24/25 Xn; R22
Resulting harmonised classification (future entry in Annex VI CLP Regulation)	Repr. 1B - H360F STOT RE 1 - H372 Acute Tox. 4 - H302	Repr. Cat. 2; R60 T; R48/23/24/25 Xn; R22

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on 09 July 2010. Parties concerned and MSCAs were invited to submit comments and contributions by 22 August 2010.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Marianne van der Hagen***
Co-rapporteur, appointed by RAC: ***Annemarie Losert***

The opinion takes into account the comments of MSCAs and parties concerned provided in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***21 February 2011,*** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The RAC Opinion was adopted by ***consensus.***

OPINION OF RAC

The RAC adopted the opinion that ***4-tert-butylbenzoic acid*** should be classified and labelled as follows:

Classification & Labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
	4-tert-Butylbenzoic acid	202-696-3	98-73-7	Repr. 1B STOT RE 1 Acute Tox. 4	H360F[1] H372 H302	GHS07 GHS08	H360F H372 H302			

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	4-tert-Butylbenzoic acid	202-696-3	98-73-7	Repr. Cat. 2; R60 T; R48/23/24/25 Xn; R22	T R: 60-22-48/23/24/25 S: 53-45		

[1] It is the view of RAC that hazard statement H360F is the most appropriate, given the available toxicological profile of ***4-tert-butylbenzoic acid***, but RAC recognised that H360 could be applied if the available criteria are applied strictly."

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by ***Germany***.

Substance for which a harmonised C&L has been agreed at TC C&L

For 4-tert-butylbenzoic acid a harmonised C&L has been agreed at TC C&L in September 2007. However, this proposal for harmonised classification submitted under the new CLP regulation procedures does not cover all the hazard classes that have been discussed and decided upon at TC C&L. The dossier submitter decided to put forward a classification proposal specifically for health effects but not for environmental effects (TC C&L concluded with N; R51-53 as well).

Acute toxicity

The following information on the acute toxicity of 4-tert-butylbenzoic acid is a copy of the relevant chapter in the background document:

Original summary of the dossier submitter
Human data on acute toxicity of 4-tert-butylbenzoic acid are not available.

In studies with rats, oral LD50 values of >550 mg/kg and <800 mg/kg bw were detected with females being slightly more sensitive than males (Hunter et al., 1965; Procter & Gamble Comp., 1986a, b; Shell, 1950). Testicular atrophy was produced in male rats exposed to a single dose of 500 mg/kg, and degeneration of the generative cells in the seminiferous tubules was observed. The ovaries of surviving female rats were of normal appearance and presented no evidence of abnormal oogenesis at microscopy (Hunter et al., 1965).

The oral LD50 for mice was determined at 568 mg/kg bw (Shell, 1950).

Based on the above data, 4-tert-butylbenzoic acid is to be classified and labelled as Xn (harmful); R22 following the criteria of Council Directive 67/548/EEC (Annex VI: LD50 >200 – 2000 mg/kg bw) and according to CLP – Regulation 2008 (Annex I, Part 3, 3.1, LD50 300 < ATE ≤ 2000 mg/kg bw) as Acute Tox. 4 – H302.

RAC conclusion

The classification proposal of the dossier submitter is in line with the previous corresponding TC C&L recommendation. During public consultation and RAC discussions there were no comments questioning the rationale for the proposed classification for acute toxicity. Thus, based on the available comparison of acute toxicity data with DSD and CLP classification criteria RAC supports the actual proposal of the dossier submitter (CLP Acute Tox. 4 H302 respectively DSD Xn; R22).

Repeated dose toxicity

The following information on the repeated dose toxicity of 4-tert-butylbenzoic acid is a copy of the relevant chapter in the background document:

Original summary of the dossier submitter
No information is available on the effects of repeated exposure in humans.
Systemic toxic effects in animals were observed:

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

  The target organs for repeat-dose toxicity of 4-tert-butylbenzoic acid were the central nervous system, liver, kidneys, testes, epididymides, hematopoietic system and the thymus.

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

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

- Nature of adverse effects in target organs

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

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

  Urinary tract toxicity
  4-tert-butylbenzoic acid affected the urinary system by all exposure routes. The tubular epithelium of the distal cortical convoluted tubules and papillary region (renal pelvis) seemed to be the primary sites of 4-tert-butylbenzoic acid toxicity. Increased diuresis, haematuria, tubular casts, regenerative epithelium, interstitial inflammation,

hyrdronephrosis and hydroureter were associated lesions that can be considered as the death-related cause in the oral study of Hunter et al. (1965).

Liver toxicity
Increased activity of serum transaminases (Shell, 1982b), speckled, enlarged appearance of the liver were consistent with the liver cell toxicity observed in all repeat-dose studies available. The increase in liver weights were considered as indicative for hepatotoxicity in those studies (HRC, 1995; Shell, 1975), where overt morphological lesions or biochemical findings could not be observed or were unknown due to the lack of examination since hepatocyte cytotoxicity in other studies were associated to increased liver weights in the other studies. Reduced serum cholesterol levels and fatty vacuolation of liver cells can be assumed to reflect a disturbance of lipid metabolism. This assumption was supported by in vitro data on isolated hepatocytes showing that 4-tert-butylbenzoic acid inhibited fatty acid synthesis and increased medium and long chain acyl CoA esters (McCune et al., 1982).

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

Toxic effects on the hematopoietic system
Signs of microcytic hypochromic anemia were found at diet concentrations of 10000 ppm (Hunter et al., 1965), at particle concentration of 525 mg/m³ (Shell, 1982b) and at 70 mg/kg bw/d of 4-tert-butylbenzoic acid applied topically (Cagen et al., 1989).

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

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

Justification for classification

<u>Oral</u>

The lowest tested concentration of 6 mg/kg bw/d in a sub-chronic study induced significant toxic effects in male and female rats. 6 mg/kg 4-tert-butylbenzoic acid, producing kidney and testis toxicity in a 90-day study (Hunter et al., 1965), is considerably lower than the critical dose of 50 mg/kg bw/d for Xn (harmful); R 48/22 (Directives 67/548/EEC, Annex VI) and is lower than 100 mg/kg bw/d for STOT Rep. 2 – H373 (CLP Regulation; 2008, Annex I, Part 3, 3.9).

6 mg/kg is below the upper limit for category 1 (≤10 mg/kg), therefore STOT Rep. 1 is warranted. In addition 6 mg/kg is also in the order of magnitude of guidance value for attribution of T; R 48/25 (5 mg/kg bw/d) for a 90-day study.

Inhalation

Kidney lesions occurred after exposure to 12.5 mg/m³ and above in a 10/11-day study in rats (Shell, 1982b). Using Haber's rule to extrapolate to a 90-day study design, 12.5 mg/m³ 4-tert-butylbenzoic acid corresponds to 1.5 mg/m³ (0.0015 mg/l) which is below the cut-off value for Xn; R48/20. Besides kidney and testes lesions, neurotoxic potential appears to be the most sensitive adverse effect that drives classification. 4-tert-butylbenzoic acid was clearly neurotoxic at concentrations of ≥106 mg/m³ at the end of a 10/11-day study in rats (Shell, 1982b). Lesions consisted of degenerations of several regions in the brain and the spinal cords and corresponding neuronal dysfunctions. Although no related microscopic lesions were observed, the lowest concentration indicative for neurotoxicity was 4.7 mg/m³. Male rats receiving this concentration during 28 days (5 h/d, 5 d/week) showed depressed arousal activity (HRC, 1995).

4.7 mg/m³ in a 28-day study corresponds to 1.57 mg/m³ (0.00157 mg/l) in a 90-day study and is markedly lower than the limit concentration for Xn; R48/20 (≤0.25 mg/l as given in Directive 67/548/EEC, Annex VI) and STOT Rep. 2 (≤0.2 mg/l according to CLP Regulation 2008).

1.57 mg/m³ (0.00157 mg/l) is also below the limit concentration for T; R48/23 (10fold below 0.25 mg/l) and the limit concentration for STOT Rep. 1 (0.02 mg/l).

Dermal

In repeated dermal toxicity studies toxic effects were observed in three organ systems: in the kidney, male reproductive organs and peripheral blood. In a subchronic study tubular dilatation and papillary necrosis of the kidneys, tubular degeneration in the testes, and signs of microcytic hypochromic anemia were found in Fischer 344 rats at 70 mg/kg bw/d Cagen et al. (1989). Toxic effects in the testes seen as degeneration of germinal epithelium were observed in male rats exposed to 60 mg/kg bw/d for a period of 28 days (Shell, 1975). Dose-related significant increases in absolute and relative liver weights were seen in female rats of all dose groups and in male rats exposed to 15 mg/kg bw/d and above. This was the most sensitive effect from which classification should be derived. The dose 7.5 mg/kg bw/d corresponds to 2.5 mg/kg bw/d in a 90-day study, which is markedly lower than the critical dose of ≤100 mg/kg bw/d for Xn, harmful; R 48/21 (Directives 67/548/EEC, Annex VI) and of ≤200 mg/kg bw/d for STOT Rep. 2 – H373 according to CLP–Regulation 2008 (Annex I, Part 3.9).

Thus, classification and labelling of 4-tert-butylbenzoic acid as T (toxic); R48/24 and in Category 1 is applicable because the criteria for STOT Rep. 1 – H372 (≤20 mg/kg bw/d) according to CLP–Regulation 2008 is fulfilled.

Based on the above data, 4-tert-butylbenzoic acid is to be classified and labelled with T (toxic) for all routes: R48/23/24/25 / STOT Rep. 1 – H372 is warranted.

RAC conclusion

The classification proposal of the dossier submitter is in line with the previous corresponding TC C&L recommendation. During public consultation there was a comment from a member state questioning the DSD classification for oral repeated dose toxicity. In the RAC discussions there were agreements on a harmonized approach on the CLP and DSD classification as T; R48/24/25 / STOT RE-1, with support from the available data. Thus, based on the available comparison of repeated dose toxicity data with DSD and CLP classification criteria RAC supports the actual proposal of the dossier submitter (CLP STOT-RE 1 – H372 respectively DSD T; R 48/23/24/25).

Reproductive toxicity

The following information on the reproductive toxicity of 4-tert-butylbenzoic acid is a copy of the relevant chapter in the background document:

Original summary of the dossier submitter
No hazard assessment for 4-tert-butylbenzoic acid with respect to developmental toxicity is possible since there are no human or experimental data available.

With regard to male fertility, several repeated dose toxicity studies with rats with different routes of application (oral, inhalation, dermal) and one oral fertility study in rats (Hoechst, 1987) are available revealing a toxic potential of 4-tert-butylbenzoic acid with induction of testicular lesions, spermatotoxic effects (reversible at test dose of 41 mg/kg) and infertility already at relatively low dosages/concentrations. Consistently and independent from route of application testes toxicity was characterised by lower absolute and relative organ weights, testes atrophy from seminiferous tubular degeneration, destruction of the germinative epithelium resulting in disturbance of spermatogenesis and in particular in loss of late spermatids.

Concern on possible spermatotoxic effects of 4-tert-butylbenzoic acid also in humans might be given but remains uncertain. A study on occupationally exposed workers provided some indication for slightly higher numbers of individuals with low sperm count (less than 20 million sperm/ml) in exposed participants compared to non-exposed participants. However the findings could be biased by other factors and uncertainty remains due to the low numbers of participants.

Hazard assessment for 4-tert-butylbenzoic acid with respect to female fertility is not possible, since there are no data available.

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

Table: NOAEL/C and LOAEL/C values from different administration routes for fertility risk characterisation[1]

Route of application (duration)	**NOAEL/C**	**LOAEL/C**	**Reference**
Oral (70 days)	1.6 mg/kg bw/d	7.9 mg/kg bw/d	Hoechst, 1987
Oral (90 days)	-	6 mg/kg bw/d	Hunter et al., 1965
Dermal (7 and 13 weeks)	35 mg/kg bw/d	70 mg/kg bw/d	Cagen et al., 1989
Dermal (28 days)	30 mg/kg bw/d	60 mg/kg bw/d	Shell, 1975

[1] Replica of Table 5 in Annex I. Please see Annex 1 for details on studies.

Inhalation (4 days (3 days rest) 3 days)	-	12.5 mg/m^3	Shell, 1982b

In some studies testes toxicity occurs at same doses where body weight gain was also significantly affected (Hoechst, 1987, Shell, 1975), which would argue for Repr. Cat 3 according to 67/548/EEC. However, there are other studies reporting that testes toxicity was evident at doses/concentration without any sign of general toxicity (Hunter et al., 1965, Cagen et al., 1989, Shell, 1982b). Due to the fact that testes toxicity was observed in some studies without significant general toxicity it could not be interpreted as secondary effect. Since a clear-cut toxic potential specifically adverse to male gonads and resulting in impaired male fertility in rats was revealed for 4-tert-butylbenzoic acid in several studies and consistently across various routes of administration the substance is to be classified and labelled with T (toxic); Repr. Cat 2 R60 according to Directives 67/548/EEC, Annex VI and Repr. 1B – H360F to CLP–Regulation 2008 (Annex I, Part 3, 3.7).

No data are available on developmental toxicity.

RAC conclusion

The classification proposal of the dossier submitter is in line with the previous corresponding TC C&L recommendation. During public consultation and RAC discussions there were no comments questioning the rationale for the proposed classification for reproductive toxicity. Thus, based on the available comparison of reproductive toxicity data with DSD and CLP classification criteria RAC supports the actual proposal of the dossier submitter (CLP Repr. 1B – H-360F respectively DSD T; Repr. Cat. 2; R60).

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1 Background Document (BD)[2]

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)

[2] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.