Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

2,4,6-tri-tert-butylphenol

EC Number: 211-989-5
CAS Number: 732-26-3; (1333-60-4); (11100-56-4); (19879-87-9); (50356-20-2); (53320-88-0)

CLH-O-0000006909-58-01/F

Adopted

8 October 2020

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: 2,4,6-tri-tert-butylphenol; [1] Reaction mass of 2,6-di-tert-butylphenol and 2,4,6-tri-tert-butylphenol; [2] Reaction mass of 2-tert-butylphenol and 2,6-di-tert-butylphenol and 2,4,6-tri-tert-butylphenol [3]
EC number: 211-989-5 [1] -[2] -[3]
CAS number: 732-26-3 [1] -[2] -[3]
Dossier submitter: Belgium

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	1
Comment received				
Based on the available data the proposal for no classification is supported as there is only limited data available. A chronic toxicity study (24 month) with limited details and histopathology only on liver, kidney and adrenals was described in which no neoplastic lesions were found. One editorial comment, there is a contradiction between table 20 (lower bw in females at highest dose) and the text below (higher body weight in females) which should be corrected.				
Dossier Submitter's Response				
Thank you for your comment and support. In the chronic toxicity study (Matsumoto K. et al., 1991), the body weight was significantly reduced in females exposed to the highest dose after 12 months of exposure (240, 274**, 253, 237 and 198** g respectively at 0, 30, 100, 300 and 1000 ppm at 12 months; 296, 297, 270, 262 and 192** g respectively at 0, 30, 100, 300 and 1000 ppm at 24 months).				
RAC's response				
Thank you for the opinion on no classification for carcinogenicity and editorial remarks.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	2
Comment received				
Based on the available data the proposal for no classification is supported. The available data showed negative results for bacterial reverse mutation assay (OECD TG 471), in				

vitro mammalian cell gene mutation test (OECD TG 476) and in vitro mammalian chromosome aberration test (Japanese guideline).
Dossier Submitter's Response
Thank you for your comment and support
RAC's response
Thank you for the opinion on no classification for mutagenicity.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
24.05.2019	Sweden		MemberState	3
Comment received				
The SE CA agrees that classification of 2,4,6-tri-tert-butylphenol for adverse effects on the development of the offspring is warranted based on the observed statistically significant dose-related increase in postnatal loss at 10 and 30 mg/kg bw/day in a combined repeated dose and reproductive toxicity screening study. Also, pup body weights were statistically significantly reduced PND 1 (11% and 10%) and PND 4 (16% and 20%) at 10 and 30 mg/kg bw/day, respectively. There were no statistically significant changes in maternal body weights during gestation and lactation, no adverse clinical observations and no indications of poor maternal care were reported. Statistically significant increased liver weights and slight to moderate liver hypertrophy were reported in dams at 10 and 30 mg/kg bw/day. However, the observed adverse effects on the offspring are not considered to be secondary non-specific consequence of the liver toxicity in dams. Thus, the SE CA suggests that classification in category 1B instead of category 2 may also be discussed.				
Dossier Submitter's Response				
Thank you for comment and your support for a classification as Repr. BE CA recognize that a classification as Repr. 1B can be more appropriate and should be discuss based on the higher percent of postnatal loss and the dose related reduce viability index.				
RAC's response				
The proposal to classify Repr. 1B is shared by RAC. Thank you for comments.				

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	4
Comment received				
Proposal for classification of Repr. 2 H361d should be changed into Repr. 1B H360D. A combined repeated dose toxicity study with reproduction/ developmental toxicity screening test (OECD TG 422) showed no adverse effect on sexual function and fertility. However, a dose-dependent, statistically significant decrease in pup weight and pup survival was observed at the mid- and high-dose group. These effects are not considered to be secondary to maternal toxicity as maternal toxicity is limited to hepatocellular hypertrophy at these dose levels, only at the high-dose 1 female showed hepatocellular necrosis.				
Dossier Submitter's Response				
Thank you for comment and your support for a classification as Repr. BE CA recognize that a classification as Repr. 1B can be discussed based on based on higher percent of postnatal loss and the dose related reduce viability index.				

RAC's response
The proposal to classify Repr. 1B is shared by RAC. Thank you for comments.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	5
Comment received				
Based on the available data the proposal for classification of Acute Tox. Cat 4 H302 is supported. After oral exposure of 2000 mg/kg bw 2 female found dead at day 1 and 3 females and 1 male were killed between day 1 and 4 after exposure, no effects were found at 200 mg/kg bw. The LD50 is estimated to be <2000 mg/kg bw.				
Dossier Submitter's Response				
Thank you for your comment and support.				
RAC's response				
Thank you for comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	6
Comment received				
Based on the available data the proposal for no classification is supported. A skin irritation study according to OECD TG 404 showed the following scores: mean erythema score: 0.22/4 and mean oedema score 0/4.				
Dossier Submitter's Response				
Thank you for your comment and support.				
RAC's response				
Thank you for comment. No classification is supported.				

OTHER HAZARDS AND ENDPOINTS – Serious eye damage/eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	7
Comment received				
Based on the available data the proposal for no classification is supported. An Eye irritation study according to OECD TG 405 showed the following scores: mean corneal opacity score: 0/4; mean iris score 0/2, mean conjunctival redness score 0.22/3; mean chemosis score 0/4.				
Dossier Submitter's Response				
Thank you for your comment and support.				
RAC's response				
Thank you for comment. No classification is supported.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	8
Comment received				
Based on the available data the proposal for classification of Skin Sens 1B is supported. A LLNA assay according to OECD TG 429 showed a dose dependent increase in SI values (1.7, 3.3 and 4.6 for 10, 25 and 50%, respectively) leading to an EC3 of 22.2%.				
Dossier Submitter's Response				
Thank you for your comment and support				
RAC's response				
Thank you for comment. Skin Sens. 1B classification is supported.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.05.2019	Germany		MemberState	9
Comment received				
Based on the available data a classification of STOT RE2 is more appropriate rather than STOT RE1. Data for a combined repeated dose toxicity study with reproduction/ developmental toxicity screening test (OECD TG 422) as well as a chronic toxicity study (OECD TG 452) are shown. In the first study increased liver weight and hepatocellular hypertrophy were observed for the high-dose in male and the mid- and high-dose in female rats. At the high-dose hepatocellular necrosis was observed with very low incidences (1 male and 1 female). In the chronic toxicity study swelling, focal necrosis and vacuolisation of hepatocytes was found from 6 month onwards at ≥25.05 mg/kg bw. However, incidences were not reported in the short study report. The dose levels from these two studies were extrapolated for classification purposes. For the combined repeated dose and reproduction screening test the dose level showing increased liver weight and hepatocellular hypertrophy were used for extrapolation (30 mg/kg bw male and 10 mg/kg bw female). For the chronic toxicity study a dose level of 25.05 mg/kg bw (exposure 24 month) was used but the values were not correctly extrapolated (the extrapolated dose for 90 days should be higher than for the 24 month study). However, for the first study (OECD TG 422) it would be more appropriate to use the high-dose for both sexes (30 mg/kg bw) as hepatocellular necrosis was observed only at this dose level, even though with a very low incidence. This would lead to an extrapolated effective dose of approximately 10 mg/kg bw male and 15 mg/kg bw female as male and female rats are dosed for different durations. Furthermore the more relevant study appears to be the chronic toxicity study, in which effects in the liver were found from 6 month onwards at ≥25.05 mg/kg bw (although incidence are not reported). Using this as a starting point and 6 month as exposure duration, the extrapolated dose should be approximately 50 mg/kg bw. As the extrapolated values are in the range of 10 < C ≤ 100 mg/kg bw a classification of STOT RE2 would be appropriate.				
Dossier Submitter's Response				
Thank you for your comment.				

In the chronic toxicity study, histopathology examination revealed swelling, focal necrosis and vacuolisation of hepatocytes without more information (the incidence was not reported in the study report). BE CA recognizes that the effective dose for the chronic toxicity study was not correctly extrapolated and that the extrapolated effective dose for exposure of 90 days is 50.10 mg/kg bw/d. Based on that, BE CA recognizes that a classification as STOT RE 2 is more appropriate.
RAC's response
Thank you for comment. Classification as STOT RE 2 is supported.