Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

6,6'-di-*tert*-butyl-2,2'-methylenedi-*p*-cresol; [DBMC]

EC Number: 204-327-1
CAS Number: 119-47-1

CLH-O-0000001412-86-288/F

Adopted

13 June 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 6,6'-DI-TERT-BUTYL-2,2'-METHYLENEDI-P-CRESOL (DBMC)

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.

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Substance name: 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol
EC number: 204-327-1
CAS number: 119-47-1
Dossier submitter: Denmark

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2018	Germany		MemberState	1
Comment received				
Results from one screening and six reliable (Klimisch 2) rodent studies on testes and sperm toxicity are sufficient to conclude Repro 1B, H360F. Therefore we support the proposal to classify DBMC as Repr. 1B, H360F as well as potency classification of the substance in "medium potency group".				
Dossier Submitter's Response				
Thank you for your support to the classification of DMBC as Repr.1BF with no SCL.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.12.2018	France		MemberState	2
Comment received				
Fertility DBMC has been shown to induce adverse effects on the male reproductive organs (decrease weight and histology) and sperm production in mice and in three strains of rats. These effects were seen at doses causing systemic toxicity such as decrease in body weight and increase in relative liver weight, generally in a moderate extent. However, it was observed without any significant signs of systemic toxicity at several occasions: dose of 50 mg/kg in the study 1 (MHWJ 1999b) and study 5 (Takahashi 2006) in both rats and mice. In addition, effects on the liver weight were observed in the mid-dose (300 ppm) of study 3 (Takagi, 1994), without effects on reproductive organs weight or histology. These observations tend to support that both effects are not linked. Overall, the effects on the male reproductive organs cannot be attributed to a secondary non-specific consequence				

of systemic toxicity.
The effects are consistently observed in the different studies and are serious effects. Fertility itself is not compromised in the OCDE 421 study but this may be attributed to the important reproductive capacity of rats and the observed effects are expected to significantly impair fertility in species with lower reproductive capacities such as humans. The classification Repr 1B for fertility is therefore supported.
The absence of SCL is also supported.

Development
It is noted that effects on foetal mortality are reported in both the developmental study (Tanaka 1990) and the OECD 421 study at the mid-dose (MHWJ, 1999). These effects were observed only in the presence of marked maternal toxicity (including death of two dams) in the developmental study. In the OECD 421 study at the mid-dose of 200 mg/kg, the maternal corrected body weight gain was decreased by 5% at delivery and it is unikely that it may explain an effect such as viability of the foetuses. In relation to dose-response, it is noted that this study is a screening study and was therefore performed with a relatively limited number of animals. This provides a low statistical power and can interfere with the detection of dose-response. However, because the effect is of small in magnitude at the mid-dose and no effect or tendency is seen at the high dose, the conclusion for no developmental classification based on absence of adequate data to conclude is supported.

Dossier Submitter's Response

Thank you for your substantiated support to the proposed classification of DBMC as repr 1BF and no classification for developmental toxicity.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
06.12.2018	Sweden		MemberState	3

Comment received

The Swedish CA supports the classification of DBMC as specified in the proposal (i.e. Repr. 1B, H360F). Based on the information presented in the CLH report and the WoE analysis (Annex II of the report), we agree that the following key effects are important in order to classify DBMC as having adverse effects on sexual function and fertility:
• Significantly reduced absolute and relative testes weight already at 42 mg/kg bw/day for a 6 months exposure period (Takagi et al., 1994);
• Adverse histopathological effects in the testes (e.g. atrophy of the seminiferous tubules, giant cell formation and degradation of step 19 spermatids) (Takagi et al., 1994; MHWJ, 1999b);
• Consistently reduced sperm count and sperm motility, and adverse effects on morphology parameters (Takagi et al., 1994; MHWJ 1996a, 1999b; Takahashi et al., 2006).

The reproduction/developmental toxicity screening test performed according to OECD and GLP guidelines shows clear evidence of adverse effects on the testes that impair fertility. The other repeated dose toxicity studies presented in the CLH report (i.e. sub-acute, sub-chronic and chronic) clearly indicate a dose-response (consistent across all studies) for male reproductive toxicity at doses and time-points that do not present signs of systemic or other types of toxicity.

Moreover, the fact that data available from several animal studies performed with

different species (i.e. rats and mice) show similar adverse effects on sexual function and fertility supports as well the classification as Repr 1B, H306F. The only sub-chronic toxicity study where no adverse effects were seen on the male reproductive system was the one performed in dogs, but the inconclusive results are attributed to having a small group size (i.e. 2 dogs/sex/dose group).

The MoA suggested by Takagi et al. 1994 (i.e. uncoupling effect in mitochondria resulting in lack of ATP) could potentially explain the adverse effects of DBMC on the testes, but no in vivo data is available to support such a hypothesis. Furthermore, there is no toxicokinetic data to indicate differences in ADME between animals and humans and thus the effects observed in animals cannot be considered irrelevant for human exposure.
The Swedish CA does not consider that the classification of DBMC as Repr. 1B, H 360F is dependent on the results of the ongoing testing proposal (TP) for an extended one-generation reproductive toxicity study (EOGRTS) as standard information requirement under the REACH regulation, as stated by the registrant. The CLH report provides data that show consistent sperm and testes effects in experimental animals, which fulfil the criteria for classification of DBMC as toxic to reproduction in category 1B for effects on sexual function and fertility.

Dossier Submitter's Response

Thank you for your substanciated support to the proposed classification of DBMC as Repr.1BF

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	Finland		MemberState	4

Comment received

Finnish Competent Authority Comments on the Proposal for Harmonised Classification and Labelling of 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol (DBMC)

The FI CA supports the DKs proposal to classify DBMC as a Repr 1B (H360F: May damage fertility) based on the dose-related adverse effects on male sexual function and fertility following exposure to DBMC.

Results from one reproductive toxicity study and several repeated dose toxicity studies in rats, ranging from 28 day to 18 months exposure at dose levels of 40-88 mg/kg bw/day and a mouse study with 2 months exposure indicate clear dose-response and temporal concordance for the reproductive toxicity on sperm related parameters and reproductive organs in male rats. No general toxicity is present or there are only slight effects, which cannot explain the specific effects on sperm and the male reproductive organs. Although there was some biological variability in response incidence and severity between different tests of the same duration, overall incidence and severity occur with increasing doses and increasing exposure time. Current information supports the criteria for classifying DBMC as Repr. 1B.

Dossier Submitter's Response

Thank you for your support to the proposed Repr. 1BF classification for DBMC.

RAC's response

Noted.