

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-benzyl-2-dimethylamino-4'-
morpholinobutyrophenone**

EC Number: 404-360-3
CAS Number: 119313-12-1

CLH-O-0000001412-86-124/F

Adopted
16 September 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-BENZYL-2-DIMETHYLAMINO-4'-MORPHOLINOBUTYROPHENONE

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-benzyl-2-dimethylamino-4'-morpholinobutyrophenone

EC number: 404-360-3

CAS number: 119313-12-1

Dossier submitter: BASF SE

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.11.2015	Germany		MemberState	1
Comment received				
The German CA supports the proposed classification as a suspected human reproductive toxicant (Repr. 2; H361d).				
Editorial Comments: <ul style="list-style-type: none">• In the CLH Report it is stated in table 1 that the substance is a racemate. In IUCLID section 1.1 and 1.2 it is stated that a multi constituent substance is given, but no information about a racemat is given. Please add this information also in the reference substance and /or in the remark field in IUCLID section 1.2				
Dossier Submitter's Response				
The information that the substance is a racemate is already maintained in the reference substance. Unfortunately the relevant pick list field is displayed neither in IUCLID section 1.1 nor 1.2. We will amend the freetext field "brief description" of IUCLID 1.2 to state "multi constituent substance (racemate)". Then the information is immediately visible.				
RAC's response				
RAC considered classification in category 1B more appropriate than in category 2 (see response to comment no. 4).				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-BENZYL-2-DIMETHYLAMINO-4'-MORPHOLINOBUTYROPHENONE

Date	Country	Organisation	Type of Organisation	Comment number
11.12.2015	Germany		Company-Manufacturer	2
Comment received				
We agree with the classification proposal for human health hazard: Repr. 2 H361d				
Dossier Submitter's Response				
The registrant appreciates the thorough review of the CLH dossier.				
RAC's response				
RAC considered classification in category 1B more appropriate than in category 2 (see response to comment no. 4).				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
10.12.2015	Netherlands		MemberState	3
Comment received				
<ul style="list-style-type: none"> • In neither the 1 generation study nor in the subacute oral toxicity studies in rats, evidence was found of an adverse effect on reproductive organs or fertility. We therefore agree with no classification for fertility. • In the 1 generation study in rats, a decreased live birth index, increased pup mortality and reduced pup weights were observed at a dose that also induced a decrease in body weight gain and liver hypertrophy in the dams. Although it is stated in the document that effects were seen especially in litters where the body weight and/or food intake of dams was affected prenatally and postnatally, this is not true for pup mortality, which is also observed in dams that gain as much weight as an average control animal. Since effects are only observed at a dose that also induces maternal toxicity, we agree that there is only some evidence of an adverse effect on development and classification as Repr. 2; H361d is considered appropriate. 				
Dossier Submitter's Response				
The registrant appreciates the thorough review of the CLH dossier.				
RAC's response				
RAC considered classification in category 1B more appropriate than in category 2 (see response to comment no. 4).				

Date	Country	Organisation	Type of Organisation	Comment number
10.12.2015	France		MemberState	4
Comment received				
We question about the involvement of maternal toxicity in the increase of stillborn. Indeed, the corrected maternal body weight cannot be calculated due to the lack of uterine and foetal weights. Furthermore, from table 18a, it seems that in a same dam, effects on body weight are not directly linked to the presence of dead pups. For liver toxicity observed in dams, do the individual data allow suggesting a link between this effect and pup mortality? These information need to be considered in the decision of the subcategory for Reprotoxicity classification.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-BENZYL-2-DIMETHYLAMINO-4'-MORPHOLINOBUTYROPHENONE

Dossier Submitter's Response
<p>The registrant appreciates the thorough review of the CLH dossier. We have reviewed the histopathology findings for individual dams of the high dose group and compared them to pup mortality. A trend with findings was not obvious. However, evaluation was difficult because there are no litters with an extreme number of dead pups; single dead pups occurred in both litters with high and low total number of pups; and because there is no extreme variability in histopathology findings.</p> <p>It also not clear if histopathology is the most sensitive parameter. A strong indicator of parental toxicity is that the slightly higher dose of 500 mg/kg bw was found to be non tolerable if given less than half of duration of the one-generation study.</p>
RAC's response
<p>RAC found neither the small reduction in maternal body weight (gain) nor the liver toxicity (adaptive in nature) to be directly causative for the developmental effects observed. It was suggested by the dossier submitter that some non-specific mechanisms related to stress in the dams may have played a role at the high dose, but RAC noted that no stress or other significant maternal effects were observed at the mid dose, whereas developmental effects were also observed at that dose in a dose-related way. Therefore the developmental effects observed were considered not to be a secondary non-specific consequence of maternal toxicity. Given that the one-generation study in which the effects were seen is a good quality study, that the effects are severe effects (in particular stillbirth and postnatal mortality) that are relevant for humans, and the statistical significance of these effects and the dose-response relation found for stillbirth, RAC considered classification in category 1B more appropriate than category 2.</p>