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-methyl-1-(4-methylthiophenyl) -2-morpholinopropan-1-one

EC Number: 400-600-6
CAS Number: 71868-10-5

CLH-O-0000001412-86-70/F

Adopted

5 June 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-METHYL-1-(4-METHYLTHIOPHENYL)-2-MORPHOLINOPROPAN-1-ONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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

Substance name: 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one
CAS number: 71868-10-5
EC number: 400-600-6
Dossier submitter: Industry (BASF SE)

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2014	France		MemberState	1
Comment received				
Clear evidence of adverse effects on development has been observed on rat's offspring and there is some evidence of an adverse effect on female fertility. Therefore, FR supports to classify the substance for human health as Repr.1B – H360Df.				
Dossier Submitter's Response				
Thank you for your comments and your support for the proposed classification.				
RAC's response				
Thank you for your support				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2014	Netherlands		MemberState	2
Comment received				
The Netherlands agrees with the classification of Repr. 1B (H360Df) based on an increased incidence in cleft palate in rats at the lowest tested dose (40 mg/kg) and the marginal reduction in fertility in female rats. We agree that there is doubt regarding the effect on fertility because the reduction in pregnancy as observed in the reproductive part of the combined study was not observed in the developmental part of the study. Further, it is not directly clear whether the reduced pregnancy rate should be considered an effect on fertility or development or is unknown. In addition, activity was reported in a qHTS assay for small molecules agonist of the estrogen receptor alpha signaling pathway (National Center for Biotechnology Information, 2014) which is indicative of possible endocrine disrupting properties and may be a possible mechanism for the observed reproductive toxicity effects. Reference: National Center for Biotechnology Information. PubChem Substance Database; SID=57244284, https://pubchem.ncbi.nlm.nih.gov/substance/57244284 (accessed on 30.09.2014)				
Dossier Submitter's Response				
Thank you for your comments and your support for the proposed classification.				
RAC's response				
Thank you for your support and your comment.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-METHYL-1-(4-METHYLTHIOPHENYL)-2-MORPHOLINOPROPAN-1-ONE

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2014	France		MemberState	3

Comment received

p. 18 Reproductive parameters section (4.11.1.1.):
Wrong values of females pregnant in control (12/12) and high dose group (13/25) are mentioned in the text and table 10. Right values are mentioned in table 12 and are extracted from Report 14860 - Research Toxicology Centre S.p.A. (Irgacure 907 combined one generation and prenatal developmental toxicity study in rats.Testing Laboratory) with 10 and 18 females pregnant in control and high dose group, respectively. There is no consequence on conclusion.

p. 20 Table 11: It could be more useful to add the dose group instead of group number (or adding a legend).

Dossier Submitter's Response

Thank you for your comments and your support for the proposed classification.

Comment to *pp. 18 Reproductive parameters section (4.11.1.1.)*:
The present study is a combined 1-Generation / developmental toxicity study according to OECD guideline 414 and 415 which examines the effects of the test item on fertility, reproductive performance and development. For this purpose, females were divided into two groups: females sacrificed by day 20 of gestation and females which were allowed to give birth (fig. 1 and 3 of the CLH report). The pregnancy status of the females was reported according to this group classification. In table 10 the number of pregnant females which were allowed to give birth is shown. Data are derived from the study report, table 1.2, pp. 35. In table 12 the number of pregnant females which were sacrificed on day 20 p.c. is shown. These data are derived from table 1.1, page 34 of the study report. A typing error occurred in table 12, high dose group: 18/23 females were proved to be pregnant (orig.: 18/24).

Please find attached the corrected version of table 11.

RAC's response

Thank you for your comment. The CLH proposal should be updated.

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Date	Country	Organisation	Type of Organisation	Comment number
24.10.2014	Belgium		MemberState	4

Comment received

For the reproductive toxicity, a combined 1-generation and prenatal developmental toxicity study in rats (following OECD guidelines 415 and 414) reveals :
• A statistically significant decrease body weight at 80 and 120 mg/kg
• An increase of external malformations of fetuses at the highest dose (120mg/kg) such as micrognathia, cleft palate, anasarca, kyphosis, … Some malformations are already present at 40 and 80mg/kg (cleft palate, anasarca).
• A repetitive increase of visceral malformations was seen at 120 mg/kg in different organs: brain (lateral, 3rd and 4th ventricle were enlarged, anencephaly), fore and hind limbs with abnormal shape, severe pelvic dilatation of kidney, cryptorchism, …
• An increase of skeletal malformations such as ossification retardation of the sternal elements, scogliosis, .. at 120 mg/kg
• A significantly decrease of the fertility index in females at 120mg/kg and an increased incidence of irregular cycle but without clear dose-relationship.
Based on the emergence of several malformations and the great number of affected animals in the combined OECD 414/415 study, together with some questionable fertility modifications, we support the classification as category 1B H360Df.

Dossier Submitter's Response

Thank you for your comments and your support for the proposed classification.

RAC's response

Thank you for your support.

Attachment to comment No 3

Table 1 Body weight females, post-coitum period

	days post-coitum period							
group	0	3	6	9	12	15	18	20
control	242,42	260,88	272,24	284,5	299,46	321,3	368,4	404,05
40 mg/kg bw	237,25	253,74	266,31	279,01	293,05	311,35	254,78	387,37
80 mg/kg bw	241,96	258,9	267,06	278,03	291,35	308,84*	343,12**	375,78
120 mg/kg bw	232,03	248,99*	260,41*	269,16**	282,04**	299,78**	339,10**	371,33**

* = p< 0.05 ** = p< 0.01