Committee for Risk Assessment

RAC

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

5 June 2015

CLH-O-0000001412-86-70/F

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

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

Chemical name:	**2-methyl-1-(4-methylthiophenyl)-2–morpholinopropan--1-one; Irgacure 907**
EC number:	**400-600-6**
CAS number:	**71868-10-5**

The proposal was submitted by **Industry** and received by RAC on **1 August 2014**.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

BASF SE 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/harmonised-classification-and-labelling-consultation*** on **9 September 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **24 October 2014**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Christine Bjørge**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonized classification and labelling was adopted on **5 June 2015** by consensus.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Entry	606-041-00-6	2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	400-600-6	71868-10-5	Acute Tox. 4 * Aquatic Chronic 2	H302 H411	GHS07 GHS09 Wng	H302 H411		
Dossier submitters proposal	606-041-00-6	2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	400-600-6	71868-10-5	Repr. 1B Acute Tox. 4 * Aquatic Chronic 2	H360Df H302 H411	GHS08 GHS07 GHS09 Dgr	H360Df H302 H411		
RAC opinion	606-041-00-6	2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	400-600-6	71868-10-5	Repr. 1B Acute Tox. 4 * Aquatic Chronic 2	H360DF H302 H411	GHS08 GHS07 GHS09 Drg	H360DF H302 H411		
Resulting Annex VI entry if agreed by COM	606-041-00-6	2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	400-600-6	71868-10-5	Repr. 1B Acute Tox. 4 * Aquatic Chronic 2	H360DF H302 H411	GHS08 GHS07 GHS09 Dgr	H360DF H302 H411		

GROUNDS FOR ADOPTION OF THE OPINION

The substance 2-methyl-1-(4-methylthiophenyl) -2-morpholinopropan-1-one is further referred to as ***Irgacure 907*** in this opinion.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's (DS) proposal

In a GLP compliant, combined one-generation developmental toxicity study conducted according to OECD guideline 414 and 415, the effects of the test substance on male and female reproductive performance and effects of prenatal exposure on the pregnant test animal and on the developing organism were investigated. Based on a dose-range finding study, the test substance was administered daily by gavage to groups of male and female rats at dosages of 0 (control), 40, 80 and 120 mg/kg bw/day. The males were dosed for 10 consecutive weeks before pairing, during pairing and until termination. The females were dosed for 2 consecutive weeks before pairing, during pairing and until Day 19 *post-coitum* (developmental part) or until weaning (fertility part), respectively.

Fertility, in general, was decreased in all treated females and significantly decreased in the high dose group. The number of implantations was decreased in the high-dose group and an increase in pre-birth loss was noted for mid- and high-dose animals. In addition, an increase in irregular oestrus cycles was noted in all treated females. The NOAEL for maternal toxicity and fertility is considered to be 40 mg/kg bw/day.

A total loss of litter on the day of parturition or on day one *post partum* (p.p.) was recorded for all high-dose females. Increased litter loss was also observed for the mid-dose females; by day 21 p.p. all pups were deceased. Furthermore, the weight of the remaining mid-dose litters was significantly reduced and a slight retardation in development was observed. Several malformations e.g. head with domed shape, cleft palate, abnormal brain development were mainly noted in the high-dose group and to a lesser extent in the mid-dose group. But malformations did also occur in individual litters of the low-dose group.

Foetal examination revealed a decrease in the number of viable young per dam for all treatment groups. Foetal weight was significantly lower in the mid- and high-dose group; mean foetal weight was decreased in high-dose offspring. In addition, the number of viable male foetuses of the mid- and high-dose group was significantly decreased. Severe external and visceral malformations were evident in all treatment groups in a dose-dependent manner. Skeletal findings were limited to the high-dose group. A NOAEL for developmental toxicity was therefore not derived. The LOAEL was considered to be 40 mg/kg bw/day.

With respect to the findings described above, the data from this animal study provided clear evidence of an adverse effect on development manifested by (total) litter loss in the mid and high-dose groups, severe structural abnormalities in all dose groups and functional deficiencies in terms of retardation and abnormal brain development. Furthermore, there was some evidence of decreased fertility and irregular cycles in all females. Classification for reproductive toxicity with Repr. 1B (H360Df) was therefore considered to reflect appropriately the developmental and fertility effects of the substance.

Comments received during public consultation

Four comments were received from Member States during public consultation. They were all supportive of the DS proposal. In addition, one MS provided a reference (National Center for Biotechnology Information, 2014) where activity was reported in a qHTS assay for small molecules agonist of the estrogen receptor alpha signaling pathway (which is indicative of possible endocrine disrupting properties and may provide a possible mechanism for the observed reproductive toxicity effects).

Assessment and comparison with the classification criteria

A combined one-generation/developmental toxicity study in rats by oral exposure and performed according to OECD TG 414 and 415 and under GLP was included by the DS. The males were dosed for 10 consecutive weeks before pairing, during pairing and until termination. The females (n=48) were dosed for 2 consecutive weeks before pairing and during pairing until Day 19 post-coitum (n=24) or until weaning (n=24 females allowed to give birth), respectively.

Sexual function and fertility

There is no indication that male fertility was affected. Testes and epididymides weights were unaffected. Regarding toxicity in females, the reproductive parameters were assessed in the study and are presented in the table below.

The fertility index (number of pregnant females/number of sperm-positive females) was decreased in a dose-related manner in all treated females (n=24 in control group, n=48 in exposed groups): 91.7%, 87.5%, 87.5% and 64.6% (statistically significant) respectively at 0, 40, 80 and 120 mg/kg bw/day (Table below).

An increase in irregular cycles was noted in all treated females (n=48). This effect is outside the historical control data (HCD) range but is not statistically significant (Table below).

Regarding the females sacrified on day 20 post coitum, the pre-implantation loss was dose-relatedly decreased at all doses and was outside the HCD range in the high-dose group. However, in the female rats identified as pregnant and allowed to give birth there were no effects reported on the number of implantations. The *corpora lutea* decreased at all doses and in a statistically significant manner but were within the HCD (Table below).

Table: Fertility parameters in females

	Control	**40 mg/kg bw/day**	**80 mg/kg bw/day**	**120 mg/kg bw/day**	**HCD[1]**
Females sacrificed on day 20 *post-coitum*					
not pregnant[2]	2/12	3/24	3/24	5/23	
pregnant → fertility %	10/12 83.3	21/24 87.5	21/24 87.5	18/23 78.3	 83.3-91.7
Corpora Lutea	17.6	15.9*	14.8*	15.2*	13.3-17.7
Females allowed to give birth					
not pregnant	0/12	3/24	3/24	12/25	
pregnant → fertility %	12/12 100	21/24 87.5	21/24 87.5	13/25 52	 83.3-91.7
All females					
not pregnant	2/24	6/48	6/48	17/48	
pregnant → fertility %	22/24 91.7	42/48 87.5	42/48 87.5	31/48 64.6*	 83.3-91.7
Irregular cycles	3/24	12/48	11/48	14/48	2-5/24

[1] five studies between 2001-2006
[2] not-pregnant rats are female rats with positive identification of mating but were found to be not pregnant.
**= significant at p<0.05*

Information regarding parental toxicity is included in the section describing "effects on development". The study included by the DS in the CLH dossier for effects on sexual function and fertility reported effects on fertility in females. The fertility is decreased in all treated females and in a statistically significant manner at the high-dose. In females which were sacrified by day 20 *post-coitum*, numbers of *corpora lutea* were statistically significantly decreased in all dose groups. In addition, 12 out of 25 females in the mated/paired group were not pregnant. These effects are not considered by RAC to be secondary non-specific concequences of parental toxicity.

Development

The developmental toxicity part of this study included examination of the dams, examination of the pups for clinical signs, body weight and development as well as examination of the foetuses for malformations and abnormalities.

Regarding the dams, no significant sign of toxity was observed during gestation or during lactation. During the gestation period, staining on the body surface was observed in some treated females. This observation continued during the *post partum* phase in the mid- and high-dose groups. In addition, hair loss and swollen abdomen were noted in high-dose females.

During the gestation period, statistically significant decreases in body weight was observed in mid- and high-dose females from day 15 to 20 and in the high-dose group from day 3 to day 20 *post coitum*. Mean group values for the mid- and high dose terminal body weight was 375.8 g and 371.5 g compared to 404.05 g in the control group (7.4% and 8.5% lower than the mean control value, respectively) in dams sacrificed on GD 20. No effects on bw gain were reported at sacrifice on GD 20. However, on GD 18 the body weight gain was decreased by 26% in the mid-dose group and by 16% in the high-dose group compared to the control group. In females allowed to give birth, no change in bw gain was reported from GD 12 to GD 20. The only change in bw gain before GD 12 was in the mid-dose group on GD 9 (2.7 g vs 3.9 g in controls) and on GD 3 in the mid-and high-dose group (5.8 g and 6.1 g vs 4.4 g in controls). Food intake was unaffected by treatment in both sexes before pairing and in females during the *post-coitum* (p.c) period.

An increased incidence in post implantation loss and pre-birth loss was observed in the mid- and high-dose groups and is presented in the table below. This increase is not dose-related but is outside of the HCD.

Table: Post-implantation loss (%) and pre-birth loss (%) for females sacrificed on day 20 *post-coitum*.

	Control	**40 mg/kg bw/day**	**80 mg/kg bw/day**	**120 mg/kg bw/day**	**HCD**
Post-implantation loss %	3.8	4.6	10.1	6.2	2.6-6.3
Pre-birth loss %[1]	8.03	8.64	17.23	14.63	3.5-6.8

[1] Pre-birth loss = (No. of visible implantations – total litter size at birth) x 100 / (No. of visible implantations)

The total number of viable offspring per litter was decreased in all treated groups when compared to controls. In addition, statistically significant decreases in the number of viable males and consequently in the percentage of males and litter weight were noted in the mid- and high-dose groups. Mean foetal weight was statistically significantly decreased at the high-dose group when compared to controls (Table below).

Table: litter data - females sacrificed on day 20 *post-coitum*

	Control	**40 mg/kg bw/day**	**80 mg/kg bw/day**	**120 mg/kg bw/day**	**HCD**
Total viable offspring/litter	15.9	14.3	12.8	13.8	12.0-15.6
Viable males %	55.3	55.0	40.8*	45.2*	48.0-54.2
Litter weight (g)	62.3	55	48.4*	48.5*	42.1-59.3
Mean foetal weight (g)	3.9	3.8	3.8	3.5*	3.5-3.8

*=$p<0.05$

Different malformations were observed in different litters at the high dose. The external malformation observed were cleft palate, anasarca, tail bent, short or swollen, short body, kyphosis, limbs (forelimbs/hindlimbs) malrotated, short or flexure and head with domed shape (Table below).

Table: External examination of foetuses of females sacrificed on Day 20 *post-coitum*

Organ	**Malformation**	**Control**	**40 mg/kg bw/d**	**80 mg/kg bw/d**	**120 mg/kg bw/d**	**HCD (%)[#]**
	No. of foetuses (litters) examined	**159 (10)**	**301 (21)**	**269 (21)**	**249 (18)**	
Forelimbs	Malrotated	0	0	0	27 (2)	n.f.
	Short	0	0	0	59 (5)	n.f.
	Flexure	0	0	0	8 (1)	n.f.
Head	Domed	0	0	7 (1)	47 (5)	n.f.
	Micrognathia	0	0	0	14 (1)	n.f.
Hindlimbs	Malrotated	0	0	1	47 (8)	n.f.
	Short	0	0	0	21 (4)	n.f.
Palate	Cleft palate	0	5 (1)	1 (1)	28 (5)	n.f.
Tail	Bent	0	0	0	46 (7)	
	Short	0	0	0	29 (3)	n.f.
Whole foetus	Anasarca	0	7 (1)	0	36 (4)	n.f.
	Short body	0	0	0	53 (4)	n.f.
	Kyphosis	0	0	0	18 (4)	n.f.

# Historical control data were provided by either the test laboratory or the breeder company
n.f. = observation not found in the historical data set

Regarding the visceral malformations (Table below), an increase in enlarged lateral, third and fourth ventricles were observed in mid- and high-dose groups. High-dose foetuses also showed cases of anencephaly and anophthalmia. Cleft palate and abnormal shape of the fore- and hindlimbs as well as short digits were detected in high-dose foetuses.

An increased incidence in pelvic dilatation of the kidneys with ureters enlarged and/or kinked was noted in all treatment groups. In addition, cryptorchism, kyphosis and short body were noted at the high-dose, as well as one case of malformation on the septum wall of the heart and on the intestine and an increased incidence of the agenesis of the pituitary gland.

Table: Visceral malformations (fixed foetus)

Organ	**Malformation**	**Control**	**40 mg/kg bw/d**	**80 mg/kg bw/d**	**120 mg/kg bw/d**	**HCD (%)[#]**
	No. of foetuses (litters) examined	**77 (10)**	**145 (21)**	**128 (21)**	**121 (18)**	
Brain	Agenesis of the pituitary	0	0	1 (1)	27 (6)	n.f.
	Lateral ventricle enlarged, extreme	0	0	14 (5)	90 (16)	n.f.
	Third ventricle enlarged, extreme	0	0	2 (1)	52 (14)	n.f.
	Fourth ventricle enlarged, extreme	0	0	8 (3)	48 (14)	n.f.

	Anencephaly	0	0	0	10 (3)	n.f.
Eye	Anophthalmia	0	0	0	1 (1)	n.f.
Palate	Cleft palate	0	2 (1)	0	19 (5)	1 (1) = 0.1%
Heart	Interventricular septum wall incomplete	0	0	0	1(1)	n.f.
Abdomen	Diaphragmatic haernia	0	0	0	1	0.04 (0.26)
Limbs	Fore- and hindlimb abnormal shape	0	0	0	26 (6)	n.f.
Kidney	Pelvic dilatation extreme	0	0	0	7 (5)	n.f.
Ureter	Enlarged extreme	0	0	1 (1)	12 (7)	n.f.
	Kinked, extreme	0	0	0	4 (2)	0.37 (2.38)
Testis	Cryptorchism	0	0	0	20 (7)	n.f.
Forelimb	Short digit	0	0	0	8 (2)	n.f.
Intestine	Protrusion intestine from abdominal cavity	0	0	0	1 (1)	n.f.
Whole Foetus	Kyphosis	0	0	0	20 (6)	n.f.
	Short body	0	0	0	16 (3)	n.f.

Historical control data were generated from either the test laboratory or the breeder company

n.f. = observation not found in the historical data set

All pups were weighed and litters in excess of 8 offspring were culled to 8 (4 males and 4 females, where possible) by a random selection on day 4 *post partum*.
Stillbirths or total litter loss was noted at the day 1 *post partum* in all high-dose females which gave birth. A significant increase in pup loss on day 1 *post-partum* and cumulative loss on days 4 and 14 *post-partum* was observed in the mid-dose group. Litter weight was significantly decreased in the mid-dose group on days 4 and 14 post-partum. In addition, decreases in the number of viable males and consequently in the percentage of males were noted for the mid-group (Table below).

Litter data

Dose group	**Total litter size (at birth)**	**Litter size live (day 1 p.p.)**	**Litter size live (day 21 p.p.)**	**Litter weight (day 1 p.p.)**	**Litter weight (day 4 p.p.)**	**% males (at birth)**	**% males (day 4 p.p.)**
Control	15.0	13.1	7.8	83.9	116.4	44.22	45.47
40 mg/kg bw/day	13.9	12.7	7.7	84.2	120.1	44.14	43.04
80 mg/kg bw/day	12.3	6.6*	0	48.2	61.5*	52.17	46.31
120 mg/kg bw/day	11.9	0	-	-	-	54.45	-

*p<0.05

No treatment-related findings were seen at necropsy performed on low and mid-dose F1 pups culled on day 4 post partum compared to controls.

Lateral ventricles or third ventricle of the brain dilated, small cerebrum with domed head and abnormal size of the urinary bladder were the findings noted in weaned pups of the low- and mid-dose groups. In individual cases, the innominate artery was not evident.

In dead pups, no milk in the stomach was observed during the necropsy. In addition, head with domed shape, hydrocephaly, dilatation of the cerebral ventricle and small cerebrum were the findings observed in the decedent pups of the mid-dose group. In the high-dose group, the pups showed forelimbs or hindlimbs short and malrotated, head with domed shape, cleft palate, micrognathia, kyphosis, tail short or bent, short body and anasarca. Bent tail was also noted in the mid-dose group. In some cases, autolysis did not allow necropsy to be performed.

Comparison with the classification criteria

No human data was available regarding effects on sexual function and fertility or on development following exposure to Irgacure 907, therefore a classification as Repr. 1A is not justified.

According to the CLP criteria *"The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate."*

Sexual function and fertility

The combined oral 1-Generation/developmental toxicity study in rats included by the DS in the CLH dossier for effects on sexual function and fertility showed that fertility is decreased in all treated females and in a statistically significant manner at the high-dose. In females which were sacrified by day 20 *post-coitum*, numbers of *corpora lutea* in treated animals are statistically significantly decreased in all dose groups. Besides, 12 out of 25 females from the mated/paired group were not pregnant. These effects are not considered to be secondary non-specific concequences of parental toxicity.

RAC considers the effects on sexual function and fertility sufficient to classify Irgacure 907 as **Repr.1B; H360F**.

Development

As regards effects on development, examined in the same study, stillbirths or total litter loss were noted in all high-dose females which gave birth. Statistically significant increases in pup loss on day 1 *post-partum* and cumulative loss on days 4 and 14 *post-partum* were observed in the mid-dose group. In addition, litter weight was statistically significantly decreased in the mid-dose group on days 1, 4 and 14 *post-partum*. Litter size and mean pup weight were also statistically significantly decreased in the mid-dose group on day 14 *post-partum*. The survival of pups was drastically decreased in the mid- and high-dose groups. Pre-weaning clinical signs showed marked mortality of the pups in the high-dose group. Statistically significant decreases in terminal body weight were observed in the high-dose males and females. Lateral ventricles of the brain

enlarged, head with domed shape limbs short or malrotated, cleft palate, anasarca and alteration of the tail were present at necropsy of the decedent pups or in pups at weaning.

The adverse effects on development are considered to be specific effects resulting from exposure to Irgacure 907 and are not considered to be secondary non-specific concequences of maternal toxicity.For developmental effects RAC agrees with the DS proposal to classify Irgacure 907 for developmental toxicity as **Repr. 1B; H360D**.

Conclusion

RAC agrees to classify Irgacure 907 as **Repr. 1B; H360DF**.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).