Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonized classification and labelling at Community 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

05 June 2015

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name: 2-methyl-1-(4-methylthiophenyl) -2-morpholinopropan-1-one

EC Number: 400-600-6

CAS Number: 71868-10-5

Index Number: 606-041-00-6

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Part A.

Part A.

1. PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one
EC number:	400-600-6
CAS number:	71868-10-5
Annex VI Index number:	600-041-00-6
Degree of purity:	> 97.0 — < 99.9 % (w/w)
Impurities:	0.1 - 3 % (w/w)

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation		
Current entry in Annex VI, CLP Regulation	Acute Tox. 4 * Aquatic Chronic 2	H302 H411	GHS07 GHS09 Warning
Current proposal for consideration by RAC	Repr.1B	H360Df	GHS08 Danger
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 4 *, Repr. 1B Aquatic Chronic 2	H302 H360Df H411	GHS07 GHS08 GHS09 Danger

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				Reason for no classification: conclusive but not sufficient for classification
2.2.	Flammable gases				Reason for no classification: conclusive but not sufficient for classification
2.3.	Flammable aerosols				Reason for no classification: conclusive but not sufficient for classification
2.4.	Oxidising gases				Reason for no classification: conclusive but not sufficient for classification
2.5.	Gases under pressure				Reason for no classification: conclusive but not sufficient for classification
2.6.	Flammable liquids				Reason for no classification: conclusive but not sufficient for classification
2.7.	Flammable solids				Reason for no classification: conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures				Reason for no classification: conclusive but not sufficient for classification
2.9.	Pyrophoric liquids				Reason for no classification: conclusive but not sufficient for classification
2.10.	Pyrophoric solids				Reason for no classification: conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures				Reason for no classification: conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water				Reason for no classification: conclusive

	emit flammable gases				but not sufficient for classification
2.13.	Oxidising liquids				Reason for no classification: conclusive but not sufficient for classification
2.14.	Oxidising solids				Reason for no classification: conclusive but not sufficient for classification
2.15.	Organic peroxides				Reason for no classification: conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	Acute Tox. 4 *, H302		Acute Tox. 4*, H302	
	Acute toxicity - dermal				Reason for no classification: conclusive but not sufficient for classification
	Acute toxicity - inhalation				Data lacking
3.2.	Skin corrosion / irritation				Reason for no classification: conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				Reason for no classification: conclusive but not sufficient for classification
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation				Reason for no classification: conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity				Reason for no classification: conclusive but not sufficient for classification
3.6.	Carcinogenicity				Data lacking
3.7.	Reproductive toxicity	Repr. 1B, H360Df			
3.8.	Specific target organ toxicity –single exposure				Reason for no classification: conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				Reason for no classification: conclusive but not sufficient for classification
3.10.	Aspiration hazard				Reason for no classification: conclusive

					but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic Chronic 2, H411		Aquatic Chronic 2, H411	
5.1.	Hazardous to the ozone layer				Reason for no classification: conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word:

Danger
Hazard statements:
H 302 Harmful if swallowed
H 411 Toxic to aquatic life with long lasting effects
H 360Df May damage the unborn child. Suspected of damaging fertility.

Precautionary statements:
No subject for Annex entry

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Irgacure 907 was registered as ELINCS at the national British authority in 1985. The test substance showed toxic effects in acute oral studies at high doses, resulting in a classification for acute oral toxicity (Xn; R22) under Directive 67/548/EEC, 16th ATP and as Acute Tox. 4 * under Regulation (EC) No. 1272/2008 in 2008. A subacute (28-day treatment) and a subchronic toxicity study were performed with the test item. The effects seen have not caused a classification for repeat-dose toxicity. None of the above studies gave evidence of the reproductive organs being affected by treatment. At this point of knowledge, the classification for human health hazard was limited to acute oral toxicity. At a tonnage level of 100 tpa, a one generation toxicity study with a teratogenic segment was proposed in 2000. This proposal was approved by the British national authority. The Reproductive Toxicity Study in rats with Irgacure 907 (combining the one-generation study and prenatal development study protocols) performed in 2004 showed adverse effects on fertility and developmental toxicity. The study was submitted to the British authorities (the relevant body for Irgacure 907 at that time) with a proposal for a new classification and labeling (Repro. Cat 3; R63). After re-evaluation of the data using the CLP criteria and feedback from national authorities and expert committees it was concluded to submit a proposal for Repr. 1B (H360Df) to the European Chemicals Agency.

2.2 Short summary of the scientific justification for the CLH proposal

In a GLP conform combined 1-Generation / developmental toxicity study according to OECD guideline 414 and 415 (Research Toxicology Centre S. p. A, 2004) 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. The test substance was administered daily by gavage to groups of male rats and female rats at dosages of 0 (control), 40, 80 and 120 mg/kg/day, based on a dose finding study. The males were dosed for 10 consecutive weeks before pairing and during pairing until termination. The females were dosed for 2 consecutive weeks before pairing and during pairing 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 possibly 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 cycle was noted in all treated females. The NOAEL for maternal toxicity and fertility is considered to be 40 mg/kg bw/day.

A total litter loss at the day of parturition or day one p.p. was recorded for all high dose females. Increased litter loss was also observed for the mid-dose females; until day 21 p.p. all pups deceased. Furthermore, weight of the remaining mid-dose litters was significantly reduced and a slight retardation in development was observed. Several malformations e.g. 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.

Fetal examination revealed a decrease in the number of viable young per dam for all treatment groups. Fetal weight was significantly lower in the mid- and high dose group; mean fetal weight was decreased in high dose offspring. In addition, the number of viable male fetuses 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 is therefore not derived. The LOAEL is considered to be 40 mg/kg bw/day.
With respect to the findings described above, the data from this animal study provide clear evidence of an adverse effect on development manifested by (total) litter loss in mid and high dose group, severe structural abnormalities in all dose groups and functional deficiencies in terms of retardation and abnormal brain development. Furthermore, there is some evidence of an adverse effect on fertility manifested by decreased fertility and irregular cycles in all females. Classification for reproductive toxicity with Repr. 1B (H360Df) is therefore considered to reflect appropriately the developmental and fertility effects of the substance.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Classification

Acute Tox. 4 *, H302

Aquatic Chronic 2, H411

Labelling

GHS07: exclamation mark

GHS09: environment

Warning

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Classification

Acute Tox. 4 *, H302

Aquatic Chronic 2, H411

Repr. 1B, H360Df

Labelling

GHS07: exclamation mark

GHS08: health hazard

GHS09: environment

Danger

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The information available revealed teratogenic and developmental toxic effects of Irgacure 907 (2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one) in rats. The effects observed include severe malformations, retardation, abnormal brain development, reduced number of live foetuses and increased pup mortality. Moreover, Ircacure 907 is suspected to have an adverse effect on fertility which was evident by significant decreased fertility and irregular oestrus cycles.

Based on the results obtained from testing, Irgacure 907 should be classified and labelled GHS08, Repr. 1B H360Df according to Regulation 1272/2008/EC (CLP). 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one is currently listed in Annex VI of the CLP regulation as Acute Tox. 4 *.

As the substance requires classification and labelling due to CMR properties, action at Community level is required to ascertain a proper handling and RMMs for this substance. Therefore, a harmonised classification and labelling for this substance is considered a Community-wide action under Article 36 of Regulation (EC) 1272/2008/EC (CLP Regulation), and it is recommended that the classification proposal is considered for inclusion in Annex VI to CLP Regulation.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

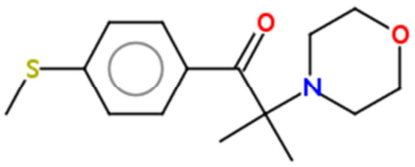
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	400-600-6
EC name:	2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one
CAS number (EC inventory):	71868-10-5
CAS number:	71868-10-5
CAS name:	1-Propanone, 2-methyl-1-[4-(methylthio)phenyl]-2-(4-morpholinyl)-
IUPAC name:	2-methyl-1-[4-(methylthio)phenyl]-2-(morpholin-4-yl)propan-1-one
CLP Annex VI Index number:	606-041-00-6
Molecular formula:	C_{15} H_{21} N O_2 S
Molecular weight range:	279.403

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one EC no.: 400-600-6		> 97.0 — < 99.9 % (w/w)	

Current Annex VI entry: Acute Tox. 4 *, Aquatic Chronic 2

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
several		0.1 – 3 %	

Current Annex VI entry: not applicable

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
No additives				

Current Annex VI entry: not applicable

1.2.1 Composition of test material

The test material is a mono-constituent substance.

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	white to light beige powder	Ciba, 2001	Visual inspection
Melting/freezing point	74.6 °C	Ciba, 1982	measured
Boiling point	349 °C	Ciba, 1983	measured
Relative density	1210 kg/m3	Ciba 1982	measured, 33°C
Vapour pressure	0.0002 Pa	Ciba, 1983	measured, 25°C
Surface tension	60 mN/m	Ciba, 1982	measured, 20°C, 10 g/l
Water solubility	0.0179 g/l	Ciba, 1983	measured, 20°C
Partition coefficient n-octanol/water	3.09	Ciba, 1982	measured, 25°C
Flash point	165°C	Ciba, 1984	measured
Flammability	not flammable	Ciba, 1983	measured
Explosive properties	none	Ciba, 1984	measured
Self-ignition temperature	No self-ignition up to the melting point of 75°C	Ciba, 1983	measured
Oxidising properties	No oxidising properties	Ciba, 1985	measured
Granulometry	D10= 9.6 µm D90= 40.9 µm	Ciba, 2002	measured
Stability in organic solvents and identity of relevant degradation products	Stability in organic solvents is not considered to be critical		Expert judgement
Dissociation constant	not applicable		
Viscosity	not applicable		

2 MANUFACTURE AND USES

2.1 Manufacture

CAS 71868-10-5 is produced by a multistep chemical reaction process starting from Thioanisol involving Friedel Crafts Acylation, chlorination and reaction with morpholine.

2.2 Identified Uses

The test substance CAS 71868-10-5 is used as photosensitive agent. In Europe it is used for use in industrial formulations of preparations containing this photoinitiator. Main applications are products like coatings, adhesives and inks for industrial and professional use. Consumer use is not supported.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Based on results obtained classification and labelling for physical-chemical properties according to Regulation 1272/2008/EC (CLP) is not justified.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Please refer to 4.1.3

4.1.2 Human information

Human information is not available.

4.1.3 Summary and discussion on toxicokinetics

Not relevant for this harmonised classification and labelling proposal

4.2 Acute toxicity

Not relevant for this harmonised classification and labelling proposal

4.3 Specific target organ toxicity – single exposure (STOT SE)

Not relevant for this harmonised classification and labelling proposal

4.4 Irritation

Not relevant for this harmonised classification and labelling proposal

4.5 Corrosivity

Not relevant for this harmonised classification and labelling proposal

4.6 Sensitisation

Not relevant for this harmonised classification and labelling proposal

4.7 Repeated dose toxicity

Not relevant for this harmonised classification and labelling proposal

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not relevant for this harmonised classification and labelling proposal

4.9 Germ cell mutagenicity (Mutagenicity)

Not relevant for this harmonised classification and labelling proposal

4.10 Carcinogenicity

Not relevant for this harmonised classification and labelling proposal

4.11 Toxicity for reproduction

Table 9: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
rat (Sprague Dawley SD) male/female **Combined 1-Generation and Prenatal developmental toxicity study in rats** **- fertility element -** oral: gavage 0, 40, 80, 120 mg/kg bw/day (actual ingested) *Vehicle*: Aqueous solution of 0.5 % carboxymethylcellulose (CMC). *Exposure*: males: for 10 consecutive weeks prior to	LOAEL (P): 80 mg/kg/day, reduced fertility, slight reduction in the number of implantations NOAEL (P): 40 mg/kg bw/day LOAEL (F1): 80 mg/kg/day, sign. increase in pup loss; sig. reduced litter size and litter weight NOAEL (F1): 40 mg/kg bw/day	1 (reliable without restriction) key study experimental result Test material (EC name): 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	Research Toxicology Centre S.p.A. (2004)

mating and thereafter through the day prior to sacrifice, females: for 2 consecutive weeks prior to mating and thereafter until the day before necropsy (Day 21 post-partum). (once daily, 7 days a week) OECD Guideline 415 (One-Generation Reproduction Toxicity Study) [OECD Guideline 414]			
rat (Sprague Dawley SD) oral: gavage **Combined 1-Generation and Prenatal developmental toxicity study in rats** **- developmental toxicity element -** 0, 40, 80, 120 mg/kg bw/day (actual ingested) Vehicle: Aqueous solution of 0.5 % carboxymethylcellulose (CMC). females: for 2 consecutive weeks prior to mating and thereafter until post-coitum day 19 (once a day, 7 days a week) OECD Guideline 414 (Prenatal Developmental Toxicity Study) and [OECD guideline 415]	LOAEL (developmental toxicity): 40 mg/kg bw/day, reduction in viable young/dam, retardation in development; external and visceral malformations NOAEL (developmental toxicity): no NOAEL could be derived LOAEL (maternal toxicity): 80 mg/kg bw/day, significant reduction in body weight and body weight gain, reduced number of corpora lutea and implantations, lower gravid uterus weight NOAEL (maternal toxicity): 40 mg/kg bw/day	1 (reliable without restriction) key study experimental result Test material (EC name): 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	Research Toxicology Centre S.p.A. (2004)

4.11.1 Effects on fertility

4.11.1.1 Non-human information

The study design

In a GLP conform combined 1-Generation / developmental toxicity study according to OECD guideline 414 and 415 (Research Toxicology Centre S. p. A, 2004) effects of the test substance on male and female reproductive performance were investigated (Figure 1). The test substance was administered daily by gavage to groups of male rats and female rats at concentrations of 0 (control), 40, 80 and 120 mg/kg/day, based on a dose range finding study. The males were dosed for 10 consecutive weeks before pairing and during pairing until termination. The females were dosed for 2 consecutive weeks before pairing and during pairing until weaning (

Figure 2). Examinations of the fertility part of this study comprised duration of estrus cycle, male and female fertility, pre-coital interval, copulatory index and number of implantations. Furthermore, organ weights of testes and epididymides were determined.

Figure 1 Study design and treatment periods

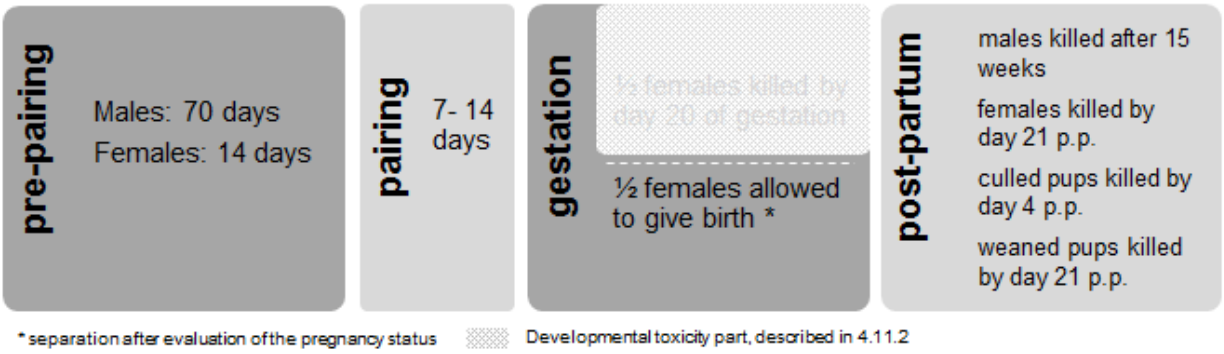


Figure 2 Group size and dose level of females

	0 mg/kg bw	40 mg/kg bw	80 mg/kg bw	120 mg/kg bw
start of treatment	24	48	48	48
killed by day 20 p.c.	12	24	24	24
killed by day 21 p.p.	12	24	24	24

p.c. = post-coitum p.p. = post-partum

Parental toxicity

One high dose male and one mid-dose female were sacrificed for humane reasons on Day 72 of the study and on Day 0 post-partum, respectively. Difficulty in parturition was noted for the female and reduced activity and pallor were noted in the male. No clinical signs of particular relevance were noted in males, throughout the treatment period, or in females before pairing. Hairloss and swollen abdomen were noted in the high dose females during the gestation period. Staining on the body surface was observed in mid- and high dose females during gestation and the post partum phase. Body weight, body weight gain and food consumption in male and female animals was comparable to control.

Reproductive parameters

Pre-coital interval and copulatory index were comparable between groups and sexes. Fertility was decreased in all treated females and significantly decreased in the high dose group. An increase in irregular cycle (not significant, out of historical range) was noted in all treated females. The number of implantation sites decreased in a dose dependent manner, with the effect still being within the historical range and considered of no statistical significance. Gestation periods were similar in the treated groups compared to controls. All dams gave birth between Day 21 and 22 post-coitum.
A total of 18 females which were allowed to give birth proved not to be pregnant at sacrifice (three low dose, three mid dose and twelve high dose group (

Table 10). The number of females with live foetuses on day 20 post-coitum was 12 in the control, 21 in the low dose, 21 in the mid dose and 13 in the high dose group (

Table 10).
There is no indication from this study that male fertility was affected. Testes and epididymides weights were unaffected and repeat-dose studies also did not indicate adverse effects on male reproductive organs.

Due to the slight reduction in the number of implantation sites, decreased fertility and irregular cycles, the LOAEL is considered to be 80 mg/kg bw/day and the NOAEL 40 mg/kg bw.

Table 10 Fertility parameters (group mean data)

Dose group	Fertility % (M)	Fertility % (F) [1]	Irregular cycles	Implantations [2]	Females pregnant / total
Control	83.3	91.7	3 / 24	16.33	12/12
40 mg/kg	100	87.5	12 / 48	15.14	21/24
80 mg/kg	95.8	87.5	11 / 48	15.05	21/24
120 mg/kg	82.6	64.6*	14 / 48	13.91	13/25
Historical control data [3]	83.3–91.7	83.3–91.7	2 – 5 /24	12.7 – 16.7	----

[1] treated animals n = 48, control n = 24 [2] females sacrificed on day 20 p.p. [3] five studies 2001 – 2006
* = significant at $p < 0.05$

4.11.1.2 Human information

This information is not available

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

The study design

In a GLP conform study the effects of prenatal exposure on the pregnant test animal and on the developing organism were investigated in a combined 1-Generation / developmental toxicity study according to OECD guideline 414 and 415 (Research Toxicology Centre S. p. A, 2004). The test substance was administered daily by gavage to female rats at dosages of 0 (control), 40, 80 and 120 mg/kg/day, based on a dose finding study. The females were dosed for 2 consecutive weeks before pairing and during pairing until day 19 post-coitum (Figure 3). Examinations of the developmental toxicity part of this study comprised examination of the dams (killed by day 20 of gestation), examination of the pups for clinical signs, body weight and development as well as examination of the fetuses for malformations and abnormalities (Figure 4).

Figure 3 Study design and treatment periods

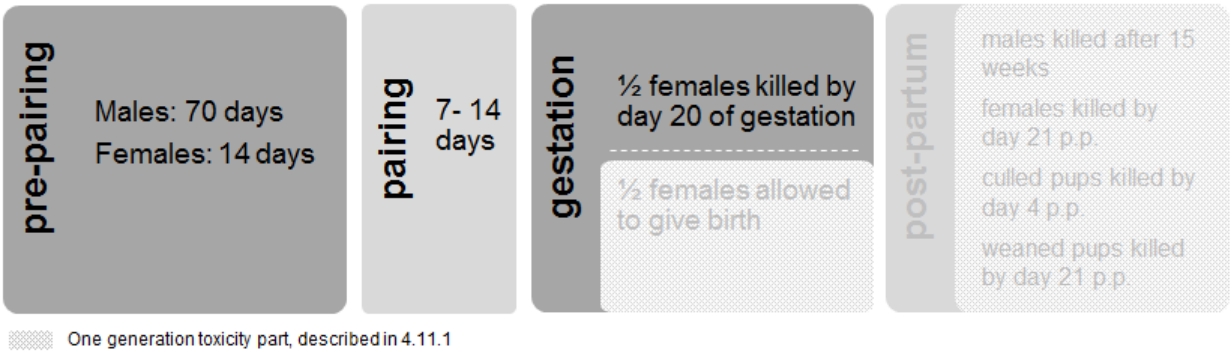


Figure 4 Examinations of the developmental toxicity part

Females (sacrificed by day 20 p.c.)	**Pups** (sacrificed by day 21 p.p.)	**Fetuses** (sacrificed by day 20 p.c.)
Corpora lutea	Litter size, litter weight, sex ratio	Body weight, sex ratio
Implantation loss	Pre-weaning development	External malformations
Uterus weight	Pre-weaning clinical signs	Visceral malformations
Clinical signs	Pup weight	Skeletal malformations
Body weight and food consumption	Necropsy	Abnormalities / variations

Maternal toxicity

Clinical signs

Before pairing, no clinical signs of toxicological significance were noted. 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.

Body weight and food consumption

During the gestation period, statistically significant decreases in body weight were observed in mid- and high dose females from day 15 to 20 and from day 3 to 20 post coitum, respectively. Mean group values for the mid- and high dose terminal body weight were 7.4% and 8.5% lower than the control mean value, respectively (Table 11). Food intake was unaffected by treatment in both sexes before pairing and in females during post-coitum period.

Table 11 Body weight females, post-coitum period

	days post-coitum period							
group	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**20**
1	242,42	260,88	272,24	284,5	299,46	321,3	368,4	404,05
2	237,25	253,74	266,31	279,01	293,05	311,35	254,78	387,37
3	241,96	258,9	267,06	278,03	291,35	308,84*	343,12**	375,78**
4	232,03	248,99*	260,41*	269,16**	282,04**	299,78**	339,10**	371,33**

* = p< 0.05 ** = p< 0.01

Pathology

A total of 13 females proved not to be pregnant at sacrifice. The number of females with fetuses on day 20 post-coitum was 10 in the control, 21 in the low dose, 21 in the mid dose and 18 in the high dose group (Table 12). The number of corpora lutea was decreased in all treatment groups. Pre-, post- and total implantation loss in all treatment groups was comparable to the control. A significant lower uterus weight was observed in the mid-dose group; the absolute uterus weight gain was decreased in mid- and high-dose females (Table 12).

Table 12 Pathology data females (females sacrificed on day 20 p.c.)

	control	40 mg/kg bw	80 mg/kg bw	120 mg/kg bw	Historical control data
Corpora lutea	17.6	15.9*	14.8*	15.2*	13.3-17.7
Implantations	16.5	15.1*	14.2*	14.7*	12.7-16.7
Pre-implantation loss %	5.9	5.6	4.0	3.2	3.5-6.8
Post-implantation loss %	3.8	4.6	10.1	6.2	2.6-6.3
Pre-birth loss %	8.03	8.64	17.23	14.63	3.5-6.8
Total implantation loss %	9.6	10.1	13.9	9.2	----
Gravid uterus weight [g]	94	83	77*	82	66.2-88.9
Absolute gain (uterus: BW ratio)	66	64	54*	55*	44.5-72.3
Females pregnant / total	10/12	21/24	21/24	18/24	-----

* $p < 0.05$

° Pre-birth loss = $\frac{\text{(No of visible implantations – total litter size at birth) x 100}}{\text{(No of visible implantations)}}$

Fetal examination

Body weight

Litter weight was statistically significantly decreased in the mid-dose and high dose group. Mean foetal weight was statistically significantly decreased in the high dose group when compared to controls (Table 13).

Sex ratio

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 (Table 13).

Table 13 Litter data – sex ratio, litter weight, fetal weight

Dose group	Total viable young / litter	Viable males %	Litter weight (g)	Mean fetal weight (g)
Control	15.9	55.3	62.3	3.9
40 mg/kg	14.3*	50.5	55.0	3.8
80 mg/kg	12.8*	40.8*	48.4*	3.8
120 mg/kg	13.8*	45.2*	48.5*	3.5*
Historical control data	12.0 – 15.6	48.0 – 54.2	42.1 – 59.3	3.5 – 3.8

* = $p < 0.05$

External malformation of fetuses

Micrognathia, cleft palate, anasarca, tail bent, short or swollen, short body, kyphosis, limbs (forelimbs and/or hindlimbs) malrotated, short or flexure and head with domed shape were observed in the high dose foetuses. In addition, cleft palate was also noted in 5 low dose foetuses and in 1 mid-dose foetus out of one litter each. Anasarca was observed in the low dose group as well as head with domed shape and hindlimbs malrotated in the mid-dose group. A total of 13 small foetuses were present; 2 each in the low and mid-dose groups and 9 in the high dose group (Table 14).

Table 14 Fetal malformations (1) (external examination, group incidence)

Organ	Malformation	Control	40 mg/kg	80 mg/kg	120mg/kg	Historical control data (%) #
	No. of fetuses (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 generated from either the test laboratory or the breeder company

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

Visceral examination of fetuses

A dome-shape observed during external examination was associated with malformations of the brain. In particular, an increased incidence of 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 in 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 15).

Table 15 Malformations (2) (fixed foetuses)

Organ	Malformation	Control	40 mg/kg	80 mg/kg	120mg/kg	Historical control data (%) #
	No. of fetuses (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	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 Lab or the Breeder company
n.f. = observation not found in the historical data set

Skeletal examination

Retardation or no ossification of the sternal elements with cases of asymmetrical ossification was observed in all treated groups. In addition, an increased incidence in general incomplete ossification of the head bones was noted in the high dose group compared to controls. Alterations of ossification in the vertebral column (thoracic, cervical lumbar and sacral vertebrae) with cases of scoliosis were observed in the high dose group.

Rudimentary 14th rib was noted in all treated groups. Displaced ribs were also observed in the high dose group. Dose-related metacarpal(s) incomplete ossification or unossified were observed in all treated groups (Table 16).

Metatarsal(s) incomplete ossification or unossified and incomplete ossification of the pubis bone were noted in the high dose group.

Table 16 Malformations (3) (skeletal findings, group incidence)

Organ	Malformation	Control	40 mg/kg	80 mg/kg	120mg/kg	Historical control data (%) #
	No. of fetuses (litters) examined	**82 (10)**	**156 (21)**	**141 (21)**	**128 (18)**	
Cervical vertebrae	Arches fused	0	0	0	1 (1)	0.04 (0.27)
Thoracic vertebrae	Scogliosis	0	0	0	22 (5)	n.f.
Rib	Displaced	0	0	0	21(5)	n.f.

# Historical control data were generated from either the test Lab or the Breeder company
n.f. = observation not found in the historical data set

Abnormalities / variations
A variety of abnormalities and/or variations were recorded especially in mid and high-dose groups, e.g. retarded / incomplete ossification at various sites of the skeleton. These abnormalities/ variations were not addressed individually in this summarized data compilation since they are of minor relevance for classification as compared to the severe teratogenic effects.

Litter data

Litter size, litter weight and sex ratio
Stillbirths or total litter loss was noted at the day of parturition or the day after parturition in all high dose females which gave birth. A significant increase in pup loss on day 1 post-partum, 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 17).

Table 17 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	13.9	12.7	7.7	84.2	120.1	44.14	43.04
80 mg/kg	12.3	6.6*	0	48.2	61.5*	52.17	46.31
120 mg/kg	11.9	0	-	-	-	54.45	-

* $p < 0.05$ adjustment of litter size on day 4 p.p. to n = 8 (4 males, 4 females)

Pre-weaning development
Slight retardation in the development of pups (Pinna detachment, hair growth and upper incisor emption) was noted in the mid-dose group (without statistical significance).

Necropsy findings
In decedent pups no milk in the stomach was observed during the necropsy. The incidence of this finding increased with the treatment. 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, these pups showed forelimbs or hindlimbs short and malrotated, head with domed shape, cleft palate, micrognathia, kyphosis, tail short or bent, short body and anasarca. Tail bent was also noted in the mid-dose group. In some cases, autolysis did not allow necropsy to be performed.
Lateral ventricles or third ventricle of the brain dilated and abnormal size of the urinary bladder in weaned pups of the low- and mid-dose groups. In individual cases, innominate artery was not evident.

4.11.2.2 Human information

Human information is not available.

4.11.3 Other relevant information

Preceding the reproductive toxicity study, a 28-day [2] and a 90-day oral toxicity study in rats [3] were performed. Dosages of 0, 30, 100, 300 mg/kg/day (28-day) and 0, 10, 25, 75, 220 mg/kg/day (90-day) were administered.

In the 28-day toxicity study, reproductive organ weights and histopathological examinations did not reveal any treatment-related findings. Mean testes weights were slightly decreased at 300 mg/kg/day absolute and relative to brain weight. This finding was not statistically flagged due to large variability and was not reported as a relevant finding. Ovaries weights were not measured in this study. In the 90-day toxicity study, male and female gonade weights were found to be unaffected.

The maternal and developmental toxicity of the test item was investigated in the rat during gestation in a Range-Finding Study [4]. The test item was administered daily by gavage to females from Day 0 through Day 19 of gestation (post-coitum) at dosages of 10, 50, 120, 160 and 250 mg/kg/day. Maternal toxicity was observed in females receiving 120, 160, and 250 mg/kg/day when compared to controls. This toxicity was demonstrated by a reduction in body weight and by total resorption in three out of eight females dosed at 250 mg/kg/day, by reduced body weight gain and by reduced total uterine weight. In addition, at 120, 160, and 250 mg/kg/day, embryonic and foetal adverse effects, anomalies and malformations were observed.

4.11.4 Summary and discussion of reproductive toxicity

In a GLP conform combined 1-Generation / developmental toxicity study according to OECD guideline 414 and 415 [1] 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. The test substance was administered daily by gavage to groups of male rats and female rats at concentrations of 0 (control), 40, 80 and 120 mg/kg/day, based on a dose finding study. The males were dosed for 10 consecutive weeks before pairing and during pairing until termination. The females were dosed for 2 consecutive weeks before pairing and during pairing until Day 19 post-coitum (developmental part) or until weaning (fertility part), respectively.
Systemic toxicity was evident by decreased body weight and body weight gain in mid- and high dose animals; food consumption was also reduced. Clinical signs were limited to the high dose females and consisted of stained body surface, alopecia and swollen abdomen. Macroscopic observation of the sacrificed animals did not reveal treatment related findings.
Fertility, in general, was decreased in all treated females and significantly decreased in the high dose group. The number of implantations was possibly 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 cycle was noted in all treated females. The NOAEL for maternal toxicity and fertility is considered to be 40 mg/kg bw/day.
In females which were sacrificed by day 20 post-coitum, **numbers of corpora lutea in treated animals are apparently differing (lower) from the numbers of the control group and display a statistical significance. By comparison with historical control data, study control values were located on the upper end of the normal range and the numbers for all treated groups are within the historical control range. Therefore, this finding is not considered to be of toxicological significance.**
A significant lower gravid uterus weight was observed in the mid-dose group; the absolute uterus weight gain was decreased in mid- and high-dose females but was still within the historical data range.
Total litter size and implantation size were reduced in all three groups. A total litter loss at the day of parturition or day one 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 deceased. Weights of the remaining mid-dose litters we significantly reduced and a decrease in the number of viable males and consequently in the percentage of males was noted for this treatment group. Additionally, slight retardation in the development of pups was noted in the mid-dose group. Several malformations e.g. 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. In decedent pups no milk in the stomach was observed during the necropsy. The incidence of this finding increased with the treatment.
Fetal examination revealed a decrease in the number of viable young per litter for all treatment groups. Litter weight was significantly lower in the mid- and high dose group; mean fetal weight was decreased in high dose offspring. In addition, the number of viable males of the mid- and high dose group was significantly decreased. Various external and visceral malformations were evident in the mid and high dose group and in individual litters of the low dose group. Skeletal findings were limited to the high dose group. A NOAEL for developmental toxicity is therefore not derived. The LOAEL is considered to be 40 mg/kg bw/day.

Several findings concerning the F1 generation underpin the low likelihood of a lactation effect but support a perinatal toxicity effect due to parental/maternal toxicity, i.e. **cumulative offspring mortality and litter loss on days 0, 1, 2 p.p. in the mid-dose group and reduced food intake in dams of the mid-dose group during the lactation period. Furthermore, observations on the**

pups during lactation („neglected pups“) and necropsy („apparently no food intake”) indicate nursing deficits of the female rats. Therefore, damage to the offspring during lactation cannot clearly be derived from the data.

4.11.5 Comparison with criteria

The substance is suspected to impair fertility in the rat which was shown in a one-generation and prenatal development toxicity study according to OECD guidelines 414 and 415. Fertility was decreased in all treated females and significantly decreased in the high dose group. An increase in irregular cycle (not significant, out of historical range) was noted in all treated females. According to 3.7.1.3. of the CLP Regulation, these effects have the potential to interfere with sexual function and fertility.

> *“Adverse effects on sexual function and fertility*
> Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.”

However, the fertility index was statistically significantly decreased at the highest dose level only and the increased incidence of irregular cycles was of questionable relevance for fertility. Furthermore, there was no clear dose-relationship of the effects. Thus, based upon the results of the present study there is some evidence of an adverse effect on fertility but not a clear indication. The substance is therefore suspected to be a human reproductive toxicant and a classification for category 2 for reproductive toxicity according to the CLP regulation is proposed.

The test item caused developmental toxicity and teratogenicity in the rat in a one-generation and prenatal development toxicity study according to OECD guidelines 414 and 415. Severe effects on embryo-fetal development including high incidence of pup mortality was observed in the mid- and high dose groups. A variety of severe teratogenic findings were mainly noted in the high dose group but malformations did also occur in individual litters of the low-dose group. According to 3.7.1.4. of the CLP Regulation, death of developing organism, structural abnormalities, altered growth and functional deficiencies are regarded as major manifestations of developmental toxicity.

> *“Adverse effects on development of the offspring*
> Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.”

The effects observed fall into all four categories of major manifestations and are therefore clear evidence of an adverse impact on development.

The slight systemic toxicity induced in the F0 generation especially in the high-dose group is not considered to be attributable to the severe degree of toxicity (teratogenicity) to the offspring, comprising all treated groups. On the other hand, the parental toxicity observed rather supports a perinatal toxicity than a lactation effect.

4.11.6 Conclusions on classification and labelling

1. Fertility

The substance shall be classified in category 2 for fertility because there is some evidence from animal studies of an adverse effect on female fertility.

2. Developmental toxicity

The substance shall be classified in category 1B for developmental toxicity because there is clear evidence from animal studies of an adverse effect on development.

It is therefore proposed to classify the substance as **Repr. 1B (H360Df)** under CLP Regulation (EC) No. 1272/2008.

RAC evaluation of reproductive toxicity

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

Summary of the Dossier submitter's proposal

In a GLP compliant combined one-generation developmental toxicity study conducted according to OECD guideline 414 and 415, 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**	**80 mg/kg**	**120 mg/kg**	**HCD[1]**

		bw/day	**bw/day**	**bw/day**	
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.

Effects on 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 CLP 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**.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier

6 OTHER INFORMATION

Not relevant for this dossier

7 REFERENCES

[1] Research Toxicology Centre S. p. A. (2004). IRGACURE 907 COMBINED ONE GENERATION AND PRENATAL DEVELOPMENTAL TOXICITY STUDY IN RATS. Testing laboratory: Research Toxicology Centre S. p. A. Report no.: 14860. Owner company: BASF SE. Report date: 2004-09-02.

[2] 28-Day Subacute Oral Toxicity Study with TK 12955 in Rats. CIBA-GEIGY Ltd., Toxicology; Project-no.821382, March 8, 1984.

[3] 3-Month Oral Toxicity Study with TK 12955 in Rats. CIBA-GEIGY Ltd., Toxicology; Project-no. 840574, October 1, 1986.

[4] Preliminary oral prenatal developmental toxicity study in rats, RTC Study no.: 9318EXT, 2003