Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

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

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

CLH-O-0000001412-86-124/F

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

16 September 2016

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name:

2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone

EC Number: **404-360-3**

CAS Number: **119313-12-1**

Index Number: **606-047-00-9**

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	**2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**
EC number:	**404-360-3**
CAS number:	**119313-12-1**
Annex VI Index number:	**606-047-00-9**
Degree of purity:	**98 – 99.9 % as a racemate**
Impurities:	**0.2% α-Benzyl-α-(dimethylamino)-3-chloro-4`-morpholinobutyrophenone** Four other known impurities at less than 0.1 or 0.05%. Sum of unspecified impurities < 0.05%

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	**Classification** **Aquatic chronic 1, H410** **Aquatic acute 1, H400** **Labelling** **GHS09, Warning**
Current proposal for consideration by RAC	**Classification** **Repr. 2 H361d** **Labelling**

	GHS08, Warning
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	**<u>Classification</u>** **Repr. 2, H361d** **Aquatic chronic 1, H410** **Aquatic acute 1, H400** **<u>Labelling</u>** **GHS08, GHS09, Warning**

1.3 Proposed harmonised classification and labelling based on CLP Regulation criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs	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 emit flammable gases				Reason for no classification: conclusive 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				conclusive but not sufficient for classification
	Acute toxicity - dermal				conclusive but not sufficient for classification
	Acute toxicity - inhalation				data lacking
3.2.	Skin corrosion / irritation				conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				conclusive but not sufficient for classification
3.4.	Respiratory sensitisation				data lacking
3.4.	Skin sensitisation				conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity				conclusive but not sufficient for classification
3.6.	Carcinogenicity				data lacking
3.7.	Reproductive toxicity	Repr. Cat 2, H361d		none	

3.8.	Specific target organ toxicity –single exposure				conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				conclusive but not sufficient for classification
3.10.	Aspiration hazard				conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic acute and chronic 1, H410, H400		Aquatic acute and chronic 1, H410, H400	

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

Labelling: Signal word: Warning

Hazard statements: H361d - Suspected of damaging the unborn child
H410 – Very toxic to aquatic life with long lasting effects

Precautionary statements: Not subject for Annex entry.

Hazard pictograms:

GHS08: health hazard

GHS09: environment

Proposed notes assigned to an entry: N.A.

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

The substance was registered as ELINCS at the national British authority in 1990. The substance showed aquatic toxicity and was not readily biodegradable resulting in a legal classification for danger to the environment (N; R50/53) under directive 67/548/EEC, 25th ATP. The EC-name of the substance was added to Annex I with a typing error. Specifically, the dash after the number four was left out and the name is currently incorrectly given as *2-benzyl-2-dimethylamino-4-morpholinobutyrophenone.* With the introduction of EC Regulation 1272/2008, the classification was translated into the hazard class 1 for both acute and chronic aquatic toxicity. No need for classification and labelling was derived from the experimental data on acute oral and dermal toxicity, subacute oral toxicity, genotoxicity in vitro, irritation and skin sensitization.

The testing requirements for the tonnage level of >100 tpa as issued by UK HSE in 2008 consisted of a one-generation study (OECD 415), environmental studies and information related to the risk assessment. By the time that the one-generation study was reported in 2011, the original registrant had been acquired by the current dossier submitting company and a new chemical regulation (REACH) had been introduced in the European Union. The one-generation study showed adverse effects on development at the high dose group and therefore, the Competent Authority in Germany was contacted. After evaluation of the data in expert committees it was concluded to submit a proposal for harmonized classification for Repro Cat 2 (H361d) to the European Chemical Agency.

2.2 Short summary of the scientific justification for the CLH proposal

Results from a one-generation reproduction toxicity study in Wistar rats (OECD 415) with oral (gavage) dosing have become available. The experimental part was conducted in 2009 and the experimental completion date / draft report preparation was in February 2011. Accompanied by adverse effects on parental animals, a reduced live birth index, increased pup mortality and reduced pup weights were observed at the highest dose group (300 mg/kg bw). Since these findings are indicators for adverse effects on reproductive performance and offspring development a classification for the endpoint was considered necessary.

In addition, correction of the name in the CLP inventory to "*2-benzyl-2-dimethylamino-4`-morpholinobutyrophenone"* is proposed.

2.3 Current harmonised classification and labelling

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

- Aquatic chronic 1
- Aquatic acute 1

2.4 Current self-classification and labelling

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

- Repr. 2
- Aquatic chronic 1
- Aquatic acute 1
- Labelling H361d, H410

RAC general comment
2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone is used as a photosensitive agent in printing inks, pigmented coatings and photopolymers for imaging applications. The substance is a racemic mixture with purity between 98 and 99.9%.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The one-generation study in rats revealed developmental toxicity of 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone. Accompanied by adverse effects on parental animals, a reduced live birth index, increased pup mortality and reduced pup weights were observed at 300 mg/kg bw.

As this triggers classification and labelling for CMR properties, article 36 of EC regulation 1272/2008 applies: A substance that fulfils the classification criteria for reproductive toxicity, category 1A, 1B or 2 shall normally be subject to harmonised classification and labelling.

Currently, the substance has a harmonized classification for aquatic toxicity (CLP Annex VI index no. 606-047-00-9). Action at the Community level is required to adapt this with the new information on developmental toxicity. This will ascertain adequate handling and use of risk minimization measurements. It is recommended that the classification proposal is considered for inclusion in Annex VI of the EU regulation 1272/2008.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

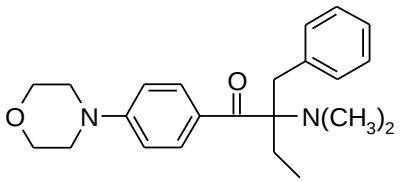
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	404-360-3
EC name:	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone
CAS number (EC inventory):	119313-12-1
CAS number:	119313-12-1
CAS name:	1-Butanone, 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl)-
IUPAC name:	2-benzyl-2-(dimethylamino)-1-[4-(morpholin-4-yl)phenyl]butan-1-one
CLP Annex VI Index number:	606-047-00-9
Molecular formula:	$C_{23}H_{30}N_2O_2$
Molecular weight:	366.5

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
2-benzyl-2-dimethylamino-4'-morpholinobutyro-phenone	99.5%	98 – 99.9%	The substance is a racemate.

- Current Annex VI entry: Aquatic chronic 1, aquatic acute 1

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
α-Benzyl-α-(dimethyl-lamino)-3-chloro-4`-morpholinobutyrophenone	0.2%	0.01-0.2%	

Current Annex VI entry: not relevant for C & L

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
none				

Current Annex VI entry: not applicable

1.2.1 Composition of test material

The substance of concern is a racemic mixture with a purity range between 98 and 99.9%.

1.3 Physico-chemical properties

Table 8: Physico-chemical properties

Property	**Description of key information**	**Reference**	**Comment (eg measured or estimated)**
Physical state	slightly yellowish powder	Ciba, 2006	Visual inspection
Melting / freezing point	113.2°C by capillary method, 114.8°C by DSC	Ciba, 1988	measured
Boiling point	decomposes at >275°C before boiling	Ciba, 1988	measured
Relative density	1210 kg/m³ at 22°C	Ciba, 1989	measured
Granulometry	MMD (width) = 55 µm (by sieving method) MMD = 11.5 µm (by laser diffraction method) D10 = 2.0 µm, D90 = 33.6 µm	Ciba, 1988	measured
Vapour pressure	≤0.0000006 Pa at 25°C (extrapolated)	Ciba, 1989	The vapour pressure was determined by thermogravimetry (Diffusion controlled evaporation)
Partition coefficient n-octanol/water (log value)	2.91	Ciba, 1988	at 25°C and at pH 6.1 (shake-flask method)
Water solubility	0.0059 g/L	Ciba, 1989	at 20°C and at pH 6.8 (flask method)
Solubility in organic solvents / fat solubility	3240 mg/100g of fat	Ciba, 1989	Measured at 37°C
Surface tension	59 - 65 mN/m	Ciba, 1988	At 20°C; filtrates of 10 g/L suspensions, Wilhelmy plate method)

Property	**Description of key information**	**Reference**	**Comment (eg measured or estimated)**
Autoflammability / self-ignition temperature	no self-ignition	Ciba, 1989	Measured
Flammability	not highly flammable upon ignition, no pyrophoric properties, does not liberate flammable gases on contact with water	Ciba, 1989	Measured (A.16)
Explosive properties	non explosive	Ciba, 1989	Measured
Oxidising properties	non-oxidizing	Ciba, 1989	Measured
Stability: thermal, sunlight, metals	thermally stable at room temperature. Solutions of the substance are sensitive to photolysis.	Ciba, 1989	Measured
Dissociation constant	pKa1= 6.3 at 25°C (of aliphatic tertiary amine) pKa2= 1.6 at 25°C (of aromatic tertiary amine)		The estimation was according to D.D. Perrin et al, pKa Prediction for Organic Acids and Bases, Chapman & Hall 1981.

2 MANUFACUTE AND USES

2.1 Manufacture

The substance is manufactured outside the EU.

2.2 Uses

2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone is used as a photosensitive agent in printing inks, pigmented coatings and photopolymers for imaging applications. These uses involve industrial

and professional workers. The mechanism of photo-curing is initiated by UV-induced cleavage of the substance.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Based on the experimental and modelled data, the substance does not need to be classified for physico-chemical properties according to EC regulation 1272/2008.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

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. Information relevant for the assessment of reproductive toxicity is provided in that chapter.

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. Overview of experimental studies on fertility

Method	**Results**	**Remarks**	**Reference**
rat (Wistar) male/female one-generation study oral: gavage 0, 30, 100 and 300 mg/kg bw/day (actual ingested) Exposure: F0 males: 110 d = ca. 16 weeks females: 126 d = 18 weeks (once daily at approximately the same time in the morning) OECD Guideline 415 (One-Generation Reproduction Toxicity Study) (adopted May 1983) GLP compliance: yes	NOAEL (general toxicity) (P): 100 mg/kg bw/day (actual dose received) (female) based on: test mat. (relative liver weight increase of 50% with central/midzonal hypertrophy, reduced food consumption and body weight gain at next higher dose level during gestation and lactation) NOAEL (general toxicity) (P): 100 mg/kg bw/day (actual dose received) (male) based on: test mat. (relative liver weight increase of 34% with central/midzonal hypertrophy) NOAEL (fertility) (P): >= 300 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (no effects observed)	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	BASF SE (2011)
rat (Wistar) male/female subacute (oral: gavage) 0, 100, 500/250 mg/kg bw (actual ingested)	NOAEL: 100 mg/kg bw/day (actual dose received) (male/female) based on: test mat.	2 (reliable with restrictions) key study	NOTOX (2009)

Method	**Results**	**Remarks**	**Reference**
Vehicle: propylene glycol Exposure: 28 days (Once daily) Dose-range-finding study with additional investigations on fertility endpoints: Histopathology of testes and epididymides for control and high dose group; slides of the testes were prepared to examine staging of spermatogenesis. Sperm motility was analyzed for all males of the control group, the intermediate dose group and the high dose group GLP compliance: yes	LOAEL: 250 — 500 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (The dose level of 500 mg/kg bw was not tolerated and reduced to 250 mg/kg after 9 days. Effects on hematology and clinical chemistry, discolouration and increased weights of kidneys and liver histopathological changes (liver, kidney, bone marrow) No effects were observed on fertility endpoints (histopathology of testes and epididymides, sperm motility and stages of spermatogenesis).	experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	
rat (Sprague-Dawley) male/female subacute (oral: gavage) 0, 10, 50, and 500 mg/kg bw/day (actual ingested) Vehicle: CMC (carboxymethyl cellulose) (5 mg/l) Exposure: 4 weeks followed by a two week recovery. (Once daily) OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) (12.05.1981) with macroscopic investigation of reproductive organs GLP compliance: yes	LOAEL: 500 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (At 500 mg/kg bw effects on haematological, biochemical and urinary parameters and organ weights were mostly slight (except liver weights) and reversible within 14 days of recovery. Alopecia was observed in all females and 1/5 males. Alopecia was observed in 1/5 females at the end of the 14 day recovery period.) NOEL: 10 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (No effects were seen at this dose	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	Hazleton (1989)

Method	Results	Remarks	Reference
	level. Slight and reversible increase in weight of adrenals for females at the next higher dose) There were no macroscopic findings on reproductive organs.		
rat (Sprague-Dawley) male/female subacute (oral: gavage) 0, 100, 300, 1000, 3000 mg/kg bw/day (actual ingested) Vehicle: CMC (carboxymethyl cellulose) (5 mg/l) Exposure: 14 days (Once daily) 14-day dose-range finding study with determination of gonad weights GLP compliance: yes	NOEL: 100 mg/kg bw/day (nominal) (male/female) based on: test mat. (No effects were observed on gonad weights; reduced body weight and food consumption and increased liver and adrenals weight in the next higher dose. Severe body weight loss and mortality/moribound condition in some animals dosed with 1000 and 3000 mg/kg bw.)	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	Hazleton (1989a)

4.11.1 Effects on fertility

4.11.1.1 Non-human information

In a GLP conform one-generation study performed according to OECD guideline 415, the test item was administered daily as a formulation in propylene glycol to groups of 20 male and 20 female young Wistar rats (F0 parental generation) by stomach tube at doses of 30, 100 and 300 mg/kg body weight/day (BASF SE 2011). Control animals were dosed daily with the vehicle only. At least 74 days after the beginning of treatment, F0 animals were mated to produce a litter (F1 rearing animals). Mating pairs were from the same dose group.

Dose levels had been chosen based on the results of a 28-day range-finding study with doses of 100 and (initially) 500 mg/kg bw. The dose-level of 500 mg/kg bw proved to be non-tolerable within ten days of dosing: Body weights dropped and food intake was reduced. Clinical findings consisted of hunched posture, piloerection, retching, rales and salivation.

During the one-generation study, the parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances. Food consumption of the F0 parental generation animals was determined once weekly (F0 males and F0 females until 10th premating week) and usually for gestation days 0 - 7, 7 - 14, 14 - 20 and lactation days 1 - 4, 4 - 7, 7 - 14 and 14 - 21. In general, body weights of F0 parental generation animals were determined once weekly. However, during gestation and lactation F0 females were weighed on gestation days (GD) 0, 7, 14 and 20 and on postnatal days (PND) 0, 1, 4, 7, 14 and 21. Estrous cycle data were evaluated for F0 generation females over a three week period prior to mating until evidence of mating occurred. Moreover, the estrous stage of each female was determined on the day of scheduled sacrifice. The F1 pups were sexed on the day of birth (PND 0) and were weighed on the first day after birth (PND 1) as well as on PND 4, 7, 14 and 21. Their viability was recorded. At necropsy, all pups were examined macroscopically (including weight determinations of brain, spleen and thymus in one pup/sex/litter). All F0 parental animals were assessed by gross pathology (including weight determinations of several organs) and affected organs were subjected to histopathological examination, special attention being paid to the organs of the reproductive system.

As a result, no histopathological findings were observed in **reproductive organs** of male and female rats in test group 3 (high dose group, 300 mg/kg bw/d). No histopathological correlate was found for the absolute and relative testes weight increase, the absolute and relative weight decrease of prostate and the absolute, but not relative weight decrease of seminal vesicles of male rats in test group 3 (300 mg/kg bw/d, tables 10 and 11). Therefore, weight changes in male reproductive organs were not considered to be treatment-related. In females, no treatment-related effects were found in reproductive organs.

Table 10: Changes (%) in absolute weights of reproductions organs in the one-generation study (BASF SE 2011)

	Males			females		
Test group	1	2	3	1	2	3
(mg/kg bw/d)	(30)	(100)	(300)	(30)	(100)	(300)
Testes	98	100	107*			
Prostate	97	100	80**			
Cauda epididymis	100	100	100			
Epididymides	97	100	100			
Seminal vesicle	97	99	87**			
Ovaries				97	98	94
Uterus				88	96	99

*p <= 0.05;**p <= 0.01, compared to control group

Table 11: Changes (%) in relative weights of reproductive organs in the one-generation study (BASF SE 2011)

	Males			Females		
Test group	1	2	3	1	2	3
(mg/kg bw/d)	(30)	(100)	(300)	(30)	(100)	(300)
Testes	103	103	113**			
Prostate	102	102	85**			
Cauda epididymis	105	102	106			
Epididymides	102	102	106			

Seminal vesicle	102	101	92			
Ovaries				98	96	97
Uterus				89	94	103

*p <= 0.05;**p <= 0.01, compared to control group

Gestation and fertility indices were within the historical range of control group animals (tables 12 and 13). The **mean number of implantation** was similar in all dose groups. Further, there were no indications from clinical examinations as well as gross and histopathology that the substance adversely affected the fertility of the F0 parental animals up to a dose of 300 mg/kg bw/day. **Estrous cycle data, mating behavior, conception**, as well as sexual organ weights and gross and histopathological findings of these organs were comparable between the rats of all test groups and ranged within the historical control data of the test facility. For all F0 parental males, which were placed with females to generate F1 pups, mating was confirmed by the female having vaginal sperm or implants in utero. Most of the F0 parental animals proved to be fertile: Absence of pregnancy in females indicating male infertility was observed for one male of the control group, one male of the low dose group, no male of the mid dose group and three males of the high dose group. Complete postimplantation loss was noted in one female of the control group and three females of the mid dose group. Postimplantation loss (%) is calculated from difference of the number of implantations and the number of pups delivered, which is then divided by the number of implantations and multiplied by 100.

Failure of pregnancy could not be attributed to the treatment by gross and histopathological examinations of the respective animals of both genders.

Table 12: Summary of cohabitation data (BASF SE 2011)

Test group (mg/kg bw/d)		0 control	1 (30)	2 (100)	3 (300)
Males placed with females	N	20	20	19	20
Mated	N	20	20	19	20
Male mating index	%	100	100	100	100
Males that did not mate	N	0	0	0	0
	%	0	0	0	0
Females pregnant	N	19	19	20[a]	17
Male fertility index (historical range 84-100%)	%	95	95	100	85
Females not pregnant	N	1	1	0	3
	%	5	5	0	15

*p<=0.05, **<=0.01, compared to control group

[a]One male of the mid dose group died prior to mating. Therefore, one male of the mid dose group mated with two females of the mid dose group.

Table 13: Summary of female reproduction data (BASF SE 2011)

Test group (mg/kg bw/d)		0 control	1 (30)	2 (100)	3 (300)
Females in study	N	20	20	20	20
Mated	N	20	20	20	20
Female mating index	%	100	100	100	100
Females pregnant	N	19	19	20	17
Duration of gestation	days	22.1	22.2	22	22.1
	SD	0.47	0.5	0	0.24
Females with implantation sites	N	19	19	20	17
Females with liveborn pups	N	18	19	17	17
Gestation index	%	95	100	85	100
Implantation sites	mean	11.6	10.9	10.6	10.6
	SD	3.25	3.43	4.27	3.84
	N	19	19	20	17
% Postimplantation loss	Mean	17.7	8.5	20.1	12.8
	SD	26.69	10.04	35.42	15.8
	N	19	19	20	17

*p<=0.05, **<=0.01, compared to control group

As part of the **subacute oral toxicity studies**, some parameters related to fertility were investigated. During the 28-day dose-range finding study with each 5 male and female rats (NOTOX 2009), histopathology of testes and epididymides was performed for control and high dose group males; slides of the testes were prepared to examine staging of spermatogenesis. Sperm motility was analyzed for all males of the control group, the intermediate dose group (100 mg/kg bw) and the high dose group (initially 500 mg/kg bw, later reduced to 250 mg/kg bw). As a result, no microscopic findings were noted on epididymides. One animal of the high dose group showed seminiferous atrophy. Sperm motility analyses revealed no abnormalities. The staging of spermatogenesis suggested normal spermatogenesis; all stages were present. No macroscopic findings on reproductive organs were noted. Weights of reproductive organs were not determined.

During the 28-day oral toxicity study performed with dose levels of 10, 50 and 500 mg/kg bw (Hazelton 1989), no macroscopic abnormalities were noted for reproductive organs, as a consequence their weights were not determined and histopathology was not performed.

Gonad weights were determined during the 14-day range-finding study performed with 100, 300, 1000 and 3000 mg/kg bw (Hazelton 1989a). Incidences of mortality occurred in females at 1000 and 3000 mg/kg bw. There were no changes in relative organ weights of gonads.

Overall, no treatment-related adverse effects on fertility were observed in the one-generation study in rats. Macro-and microscopic data of subacute oral toxicity studies does not give rise of concern to adverse effects on reproductive organs.

4.11.1.2. Human information

Human information is not available.

4.11.2. Developmental toxicity

Table 14. Overview of experimental studies on developmental toxicity

Method	Results	Remarks	Reference
rat (Wistar) male/female one-generation study oral: gavage 0, 30, 100 and 300 mg/kg bw/day (actual ingested) Exposure: F0 males: 110 d = ca. 16 weeks females: 126 d = 18 weeks (once daily at approximately the same time in the morning) OECD Guideline 415 (One-Generation Reproduction Toxicity Study) (adopted May 1983) GLP compliance: yes	NOAEL (general toxicity) (P): 100 mg/kg bw/day (actual dose received) (female) based on: test mat. (relative liver weight increase of 50% with central/midzonal hypertrophy, reduced food consumption and body weight gain at next higher dose level during gestation and lactation) NOAEL (general toxicity) (P): 100 mg/kg bw/day (actual dose received) (male) based on: test mat. (relative liver weight increase of 34% with central/midzonal hypertrophy at next higher dose level) NOAEL (reproductive performance and developmental toxicity) (F1): 100 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (live birth index 94% (range 95-100%), pup mortality and reduced pup weights at 300 mg/kg bw)	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	BASF SE (2011)

4.11.2.1 Non-human information

In a GLP conform one-generation study according to OECD guideline 415, the test item was administered daily as formulation in propylene glycol to groups of 20 male and 20 female young Wistar rats (F0 parental generation) by stomach tube at doses of 30, 100 and 300 mg/kg body weight/day (BASF SE 2011). Control animals were dosed daily with the vehicle only (propylene glycol). At least 74 days after the beginning of treatment, F0 animals were mated to produce a litter (F1 rearing animals). Mating pairs were from the same dose group.

Dose levels had been chosen based on the results of a 28-day range-finding study with doses of 100 and (initially) 500 mg/kg bw (NOTOX 2009). The dose-level of 500 mg/kg bw proved to be non-tolerable within ten days of dosing: Body weights dropped and food intake was reduced. Clinical findings consisted of hunched posture, piloerection, retching, rales and salivation.

During the one-generation study, the parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances. Food consumption of the F0 parental generation animals was determined once weekly (F0 males and F0 females until 10th premating week) and usually for gestation days 0 - 7, 7 - 14, 14 - 20 and lactation days 1 - 4, 4 - 7, 7 - 14 and 14 - 21. In general, body weights of F0 parental generation animals were determined once weekly. However, during gestation and lactation F0 females were weighed on gestation days (GD) 0, 7, 14 and 20 and on postnatal days (PND) 0, 1, 4, 7, 14 and 21. Estrous cycle data were evaluated for F0 generation females over a three week period prior to mating until evidence of mating occurred. Moreover, the estrous stage of each female was determined on the day of scheduled sacrifice. The F1 pups were sexed on the day of birth (PND 0) and were weighed on the first day after birth (PND 1) as well as on PND 4, 7, 14 and 21. Their viability was recorded. At necropsy, all pups were examined macroscopically (including weight determinations of brain, spleen and thymus in one pup/sex/litter). All F0 parental animals were assessed by gross pathology (including weight determinations of several organs) and affected organs were subjected to histopathological examination, special attention being paid to the organs of the reproductive system.

Mid- and high-dose females had a significantly increased number of stillborn pups and, at the high dose only, a **decreased live birth index** indicating an adverse effect of the test compound on reproductive performance at this dose level (table 15). For the mid-dose group both parameters were well within the historical range of the test facility and no adverse effects on postnatal development were observed (table 17). The mean number of pups delivered per dam was higher in the mid dose group than in the control group (11.2 versus 10.8); accordingly the apparent reduction of the live birth index at the mid dose is considered to be an incidental finding.
For all live born pups, no test substance-induced signs of developmental toxicity were noted at dose levels as high as 100 mg/kg bw/d. Postnatal survival as well as development of the offspring of these test groups until weaning remained unaffected by the test substance (table 16). Furthermore, clinical and/or gross necropsy examinations of the F1 revealed no adverse findings.
Pup mortality was statistically significantly increased and pup body weights were statistically significantly reduced in the high-dose group (300 mg/kg bw/d) (tables 15 -17). The number of live pups per litter as well as the total number of pups explicitly discriminates the high-dose group from the lower dose groups and controls. Pup mortality was increased during the first 4 days after birth. Both findings are regarded as treatment-related developmental toxicity (pup mortality) and slight delay of postnatal development (decreased pup body weights). However, **it should be noted that the respective findings were seen especially in litters where the dams prenatally and postnatally showed a clear reduction of body weights/body weight gain, and/or their food intake was affected**. These findings were noted exclusively in the high-dose group. In the high-dose female

population, six dams that had a body weight gain below the group mean value included the only two dams with total litter loss and three dams with small litter (table 18a). The small litter size itself may well have contributed to the lower body weight of the dams. However, the study design does not allow for quantitatively discriminating of parental versus litter toxicity. Gravid uterine weights or fetal weighs are not available so that a corrected maternal body weight gain cannot be calculated. The group mean value for body weight gain at the end of the gestation period was 83.5 g (approx. - 15% compared to controls, value = 97.7 g). Several of the six animals with body weight gains below average have individual body weight gain values that amount to only 50 to 70% of the group mean. With this reduction, the internationally acknowledged criteria for the maximum tolerated dose (-10%) is exceeded.

Secondary to the reduced pup body weights, lower weights of spleen and thymus as well as lower absolute and higher relative brain weights were noted in these offspring, these effects were not regarded as adverse or toxicologically relevant findings. Any other developmental parameters such as postnatal survival from postnatal day four remained unaffected by the test substance.

Table 15: Female delivery data

Dose group	Number of litters	Females with all stillborn pups	Females with stillborn pups[a] N (%)	Pups delivered per dam (mean)	Live birth index (%)	Stillborn pups N (%)	Viability index N (%)	Lactation index N (%)
Control	18	0	0 (0)	10.8	100	0 (0)	194 (100)	134 (100)
30 mg/kg	19	0	1 (5.3)	10.1	99	2 (1.0)	185 (98)	139 (100)
100 mg/kg	17	0	5 (29)*	11.2	97	6 (3.2)*	181 (98)	129 (99)
300 mg/kg	17	0	8 (47)*	9.5	94	9 (5.6)*	131 (86)*	103 (99)
Historical data			n.a.	9.3 - 12.8	95–100	(0–4.5)	(94–100)	(94–100)

*p ≤0.05, compared to control group; [a]The historical range is not available because this parameter depends on the litter size.

Table 16 Incidence of postnatal mortality (pups died, sacrificed moribund or cannibalized)

Test group (mg/kg bw/d)		0 (control)	1 (30)	2 (100)	3 (300)
Day 0	N	0	1	0	4
	%	0	0.5	0	2.6
Days 1 to 4	N	0	3	3	18
	%	0	1.6	1.6	12
Days 5 to 7	N	0	0	1	0
	%	0	0	0.5	0
Days 8 to 14	N	0	0	0	1
	%	0	0	0	0.7
Days 15- 21	N	0	0	0	0
	%	0	0	0	0
Pups surviving days 0 -4	N	194	185	181	131**
Pups surviving days 4 to 21	N	134	139	129	103

Table 17: Maternal body weight at the end of lactation and pup weights and numbers – group means

Dose group	BW (g) day 21p.p.	Live pups/ litter Day 1 (N)	Pups Day 1 (M+F) (g)	Pups Day 4 (M+F) (g)	Pups Day 7 (M+F) (g)	Pups Day 14 (M+F) (g)	Pups Day 21 (M+F) (g)
Control	273.0	10.8	6.3	9.3	14.7	29.3	46.6
30 mg/kg	274.5	9.8	6.3	9.5	15.0	29.5	46.3
100 mg/kg	278.6	10.7	5.9	8.8	14.0	28.1	44.3
300 mg/kg	260.3*	7.8	5.5*	7.8*	11.1*	22.6*	36.9*
Historical control range	226.7 – 307.7	9.3 – 12.8	5.8 – 6.9	8.6 – 10.6	13.1 – 17.3	25.5 – 33.4	41.3 – 53.7

*p <= 0.05;**p <= 0.01, compared to control group

Table 18a: Body weight gain and number of live and dead pups for high-dose group dams.

	Body weight gain [g]						
Female no.	GD 0-7	GD 7-14	GD 14-20	GD 0-20	Number of live pups	Number of dead pups	Total number of pups
161 no implants*	15.6	1.4	-4.1	12.9			0
162	19.1	24.4	32.6	76.1	7	1	8
163	11	19.7	25.1	55.8	4	1	5
164	25.4	29.3	50.1	104.8	11	1	12
165	19.1	32.1	56.9	108.1	13	1	14
166	20.9	23.4	49.3	93.6	13	0	13
167	30.4	20.5	48	98.9	9	2	11
168	25.5	28.5	59	113	11	0	11
169	12.4	15.2	20.5	48.1	3	0	3
170	29.3	5.9	6.8	42	1	0	1
171	28.1	22.4	57.4	107.9	14	0	14
172	22.9	19.1	46.8	88.8	8	1	9
173	17.1	25.6	30.8	73.5	7	1	8
174	16.5	8.3	33.3	58.1	5	0	5
175	13.4	19.7	43.8	76.9	11	0	11
176 no implants*	27.4	5.5	2.1	35			0

177	27.1	23.6	58.7	109.4	13	0	13
178 no implants*	15.6	7.9	-7.6	15.9			0
179	11.3	19.7	51.5	82.5	13	0	13
180	17.8	19	45.8	82.6	10	1	11
Mean	20.4	21	42.1	83.5			
SD	6.43	6.76	14.98	22.57			
N	17	17	17	17			

*excluded from mean

Table 18b: Body weight gain and number of live and dead pups for control group dams.

	Body weight gain [g]						
Female no.	GD 0-7	GD 7-14	GD 14-20	GD 0-20	Number of live pups	Number of dead pups	Total number of pups
101	23.8	31.6	64.5	119.9	14	0	14
102	26.4	25.8	29.8	82	4	0	4
103	22.8	28.4	55.4	106.6	13	0	13
104	23.6	22.4	59.9	105.9	12	0	12
105	26.4	24.4	48.6	99.4	9	0	9
106	27.8	29.2	57.9	114.9	12	0	12
107	30.9	24.2	59.4	114.5	12	0	12
108	25.1	28.9	53.1	107.1	14	0	14
109	19.1	20.5	46.1	85.7	10	0	10
110	16.2	21.2	49.6	87	11	0	11
111	23.8	24.2	56.7	104.7	12	0	12
112	17.7	21.6	53.0	92.3	11	0	11
113 no implants*	21.7	-3.2	-5.5	13			0
114	22.6	23.6	50.0	96.2	12	0	12
115, implants, no pups	14.6	0.6	19.8	35	0	0	0
116	25.8	20.4	26.6	72.8	2	0	2
117	23.4	21.2	57.7	102.3	12	0	12
118	26.9	32.0	47.1	106	10	0	10
119	28.6	21.9	57.8	108.3	12	0	12
120	36.4	22.3	56.2	114.9	12	0	12
Mean	24.3	23.4	50.0	97.6			
SD	5.14	6.63	12.03	19.6			
N	19	19	19	19			

*excluded from mean

Clinically, toxicity was noted in the F0 females at 300 mg/kg bw/d. Body weights were lower during gestation and lactation (tables 19 and 20). Lower body weight gains were most prominent during gestation (table 21). Food consumption was reduced up to 20% during lactation (table 22). All test-item treated animals showed salivation after treatment from study week 5 onwards. Although all animals were affected at least once during the study the daily incidence for salivation was higher in the mid and high dose group than in the low dose group

Table 19: Mean maternal body weights during gestation

Test group (mg/kg bw/d)		0 Control	1 (30)	2 (100)	3 (300)
Day 0	MEAN	218.10	217.80	224.90	209.20
	S.D.	10.80	14.75	15.03	12.46
	N	19	19	20	17
Day 7	MEAN	242.40	241.40	247.90	229.6*
	S.D.	11.82	14.12	16.62	13.81
	N	19	19	20	17
Day 14	MEAN	265.80	265.60	270.60	250.6*
	S.D.	15.12	14.98	16.30	18.58
	N	19	19	20	17
Day 20	MEAN	315.80	311.70	314.50	292.7*
	S.D.	23.46	22.96	26.97	28.58
	N	19	19	20	17

*p<=0.05, compared to control group

Table 20: Mean maternal body weights during lactation

Test group (mg/kg bw/d)		0 Control	1 (30)	2 (100)	3 (300)
Day 0	MEAN	248.8	246.4	252.4	232.0*
	S.D.	14.4	12.46	15.32	18.17
	N	18	19	17	17
Day 1	MEAN	244.3	246.2	252.6	229.4**
	S.D.	15	11.89	15.23	13.44
	N	18	19	17	17
Day 4	MEAN	255.2	259.1	263.3	240.6*
	S.D.	15.94	11.81	16.1	14.08
	N	18	19	17	17
Day 7	MEAN	266.2	264.3	269.9	248.0**
	S.D.	16	11.4	15.16	14.6
	N	18	19	17	17
Day 14	MEAN	280.2	278.2	285.9	256.7**
	S.D.	18.3	13.76	15.54	18.23
	N	18	19	17	17
Day 21	MEAN	273	274.5	278.6	260.3*
	S.D.	11.67	13.25	10.02	17.71
	N	18	19	17	17

*p<=0.05, **<=0.01, compared to control group

Table 21: Mean maternal body weight changes during gestation and lactation (g)

Test group (mg/kg bw/d)		0 control	1 (30)	2 (100)	3 (300)
Gestation Day 0 to 7	MEAN	24.30	23.60	23.00	20.40
	S.D.	5.14	4.87	6.29	6.43
	N	19	19	20	17
Gestation Day 7 to 14	MEAN	23.40	24.20	22.70	21.00
	S.D.	6.63	7.35	6.62	6.76
	N	19	19	20	17
Gestation Day 14 to 20	MEAN	50.00	46.10	43.90	42.10
	S.D.	12.03	12.21	19.87	14.98
	N	19	19	20	17
Gestation Day 0 to 20	MEAN	97.70	93.90	89.60	83.50
	S.D.	19.66	19.09	25.51	22.57
	N	19	19	20	17
Lactation Day 0 to 1	MEAN	-0.5	-0.2	0.3	-2.6
	S.D.	5.69	8.75	7.51	9.09
	N	18	19	17	17
Lactation Day 1 to 4	MEAN	11	12.9	10.7	11.2
	S.D.	7.87	5.14	7.14	5.9
	N	18	19	17	17
Lactation Day 4 to 7	MEAN	11	5.2**	6.5*	7.4
	S.D.	6.23	4.06	4.56	5.8
	N	18	19	17	17
Lactation Day 7 to 14	MEAN	13.9	13.9	16.1	8.7
	S.D.	8.35	8.8	9.24	8.17
	N	18	19	17	17
Lactation Day 14 to 21	MEAN	-7.2	-3.7	-7.3	3.6**
	S.D.	10.86	7.86	9.16	6.58
	N	18	19	17	17
Lactation Day 0 to 21	MEAN	28.2	28.1	26.3	28.3
	S.D.	10.94	11.79	9.77	13.49
	N	18	19	17	17

*p<=0.05, **<=0.01, compared to control group

Table 22: Mean maternal food consumption during lactation (g/animal/day)

Test group (mg/kg bw/d)		0 control	1 (30)	2 (100)	3 (300)
DAYS 1 to 4	MEAN	27.2	26.70	26.30	23.1*
	S.D.	5.21	4.05	4.58	5.07
	N	18	19	17	17
DAYS 4 to 7	MEAN	34.3	34.40	33.80	28.1**
	S.D.	5.09	5.72	5.29	5.35
	N	18	19	17	17
DAYS 7 to 14	MEAN	43.5	43.10	44.20	34.9**
	S.D.	7.45	6.81	5.71	9.05
	N	18	19	17	17
Days 14 - 21	MEAN	54.3	52.90	54.00	44.3**
	S.D.	8.70	7.83	6.25	12.95
	N	18	19	17	17
Days 0 - 21	MEAN of MEANS	39.80	39.30	39.60	32.60
	S.D.	11.76	11.32	12.13	9.22
	N	4	4	4	4

*p<=0.05, **<=0.01, compared to control group

Regarding adverse effects on **pathology**, the **liver** of males and females of test groups 2 (100 mg/kg bw/d) and 3 (300 mg/kg bw/d) was affected by a significant and dose-dependent weight increase (tables 22 and 23). In all animals of test group 3 (300 mg/kg bw/d) the weight increase correlated with central/midzonal hepatocellular hypertrophy (5 minimal and 15 slight for males, 10 minimal and nine slight for females). Brown gold and fine granular pigment storage in central hepatocytes occurred in one male at the low dose group, three males at the high dose group and 11 females of the high dose group. The pigment most probably accounted for the gross "green/brown" liver discoloration (table 25). All of these findings were related to treatment and the effects on liver at 300 mg/kg bw are considered as adverse. No histopathological correlate was found for the liver weight increase in test group 2 (100 mg/kg bw/d), which was regarded as adaptive.

In the **glandular stomach** of males and females of test groups 2 (100 mg/kg bw/d) and 3 (300 mg/kg bw/d), minimal to slight mucosal hyperemia correlated with "red focal discolorations" observed at necropsy in some animals (table 25). Males were more affected than females and showed a clear dose relationship in test group 3 (300 mg/kg bw/d). Mucosal hyperemia was attributed to a local effect due to treatment but was regarded as not adverse. Pathology and the delayed onset of salivation support the hypothesis that salivation was likely to be subsequent to local irritating effects of the test substance in the fore- and glandular stomach. It is possible that reduced food consumption and weights/body weight gain in females may have been secondary to these local effects. However, local effects on stomach were more pronounced in males whereas effects on food consumption and body weight were only observed in females.
The dose-dependent discoloration of kidneys (table 25) was determined to be non-adverse upon histopathology investigations.

Table 23: Changes (%) in absolute liver weights in the one-generation study (BASF SE 2011)

	Males			females		
Test group	1	2	3	1	2	3
(mg/kg bw/d)	(30)	(100)	(300)	(30)	(100)	(300)
Terminal body weight				99	102%	96%*
Liver	95	109	126**	102	114**	144**

*p <= 0.05;**p <= 0.01, compared to control group

Table 24: Changes (%) in relative liver weights in the one-generation study (BASF SE 2011)

	Males			Females		
Test group	1	2	3	1	2	3
(mg/kg bw/d)	(30)	(100)	(300)	(30)	(100)	(300)
Liver	101	110**	134**	103	112**	150**

*p <= 0.05;**p <= 0.01, compared to control group

Table 25: Gross lesions in the one-generation study (BASF SE 2011)

	Males				Females			
Test group	0	1	2	3	0	1	2	3
(mg/kg bw/d)	control	(30)	(100)	(300)	control	(30)	(100)	(300)
Number of animals	20	20	20	20	20	20	20	20
Liver:								
Discoloration, green brown/dark brown			6	5			5	17
Enlarged			5	14			3	19
Kidneys:								
Discoloration, green brown			11	19			2	19
Glandular stomach:								
Discoloration, red			4	15	2		5	3

Indication of stress in dams can be gained from the histopathology investigation of the adrenal glands. In the high dose group (300 mg/kg bw/d), cortical cells with condensed eosinophilic cytoplasm devoid of lipid vacuoles in the zona fasciculata correlated with significantly increased organ weights (absolute/ relative: 122% / 127%). These findings may represent ACTH-induced depletion related to stress (Hamlin II and Banas, 1990). In the mid dose group (100 mg/kg bw/d), the weight of the adrenal glands was statistically increased (abs. / rel.: 115% / 113 %) but without any histopathological correlate. These findings were interpreted as treatment-related, but secondary adaptive. No treatment-related findings were seen in females of the low dose group, and no effects had been observed in the range-finding study.

Males were less sensitive. No histopathological correlate was found in the adrenal glands of male animals of the high dose group, which had a statistically significant relative glandular weight increase (112%) within the historical control range.

4.11.2.2. Human information

Human information is not available.

4.11.3 Other relevant information

The findings on systemic toxicity observed in the one-generation study are consistent with those of the subacute studies. A subacute oral toxicity study following OECD 407 (adopted 1981) and GLP and its dose-range finding study were performed in 1989. In preparation for the one-generation study, a 28-day extended GLP-compliant dose-range-finding study was performed in 2009. The studies in 1989 were performed in Sprague-Dawley rats using 0.5 % CMC as vehicle. The newer study and the one-generation study were performed in Wistar rats using propylene glycol as vehicle. The studies are listed in table 9 since they contain some information in on reproductive organs. For details it is referred to the robust study summaries in the registration dossier.

These studies consistently show that 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone causes a strong increase in liver weight up to a certain dose level. If that dose level is exceeded, the most prominent effect quickly becomes reduced food consumption and body weight loss. The actual dose level of this threshold appears to be influenced by vehicle and/or rat strain. Whereas the dose level of 500 mg/kg bw was tolerated without effects on body weight in the 28-day study in 1989, it resulted in a strong decrease in food consumption and body weight loss within 9 days of dosing in 2011. This was accompanied by hunched posture, piloerection, retching, rales and salivation.

In the older subacute toxicity study, doses of 0, 10, 50 or 500 mg/kg bw/day of test article were administered daily via gavage to each five rats of both sexes for 28 days (Hazleton 1989). Satellite groups with a recovery period of 14 days were included. At the dose level of 500 mg/kg bw/day mainly increases in organ weights (liver, kidney and adrenals) and very slight changes in blood and urine parameters were seen. These effects, together with green and mottled kidneys as well as some mottled livers, were considered as treatment related, but were fully reversible during the recovery period. Alopecia was observed in high dose group females starting week 2 and males starting week 4. Alopecia was not fully reversible in females. Relative increase in liver weight was 41% for males and 87% for females, respectively. Histopathology did not reveal abnormal findings. The NOEL was set on 10 mg/kg bw/day, based on a slight and reversible increase in absolute (+23%) and relative weight (+19%) of the adrenal glands in females at 50 mg/kg bw.

The corresponding dose-range-finder study used doses of 100, 300, 1000 and 3000 mg/kg bw for 14 days. Mortalities were observed in group 4 (1000 mg/kg bw) and 5 (3000 mg/kg bw) animals: one group 4 female and 3 group 5 females were killed between the third and the fifth day of treatment (Hazleton 1989a) after a marked body weight loss. At the clinical observations, the group 4 animals showed slight subdued behavior from day 3 to day 9 of treatment. In group 5, subdued behavior was observed before the third administration in both sexes with ataxia in females. After treatment, ventral decubitus and tremors were observed in both sexes with hypersalivation in females. These signs were reduced with the time. Alopecia or stained fur was observed in some group 3, 4 and 5 females. At terminal sacrifice, no abnormalities were observed at macroscopic examination except alopecia in some group 3 and 4 animals, stained fur in group 5 females and enlarged liver more frequently in

treated animals. Absolute and relative adrenal weights were increased in group 4 and 5 males and in group 3, 4 and 5 females. Liver weights were increased in all treated group with a dose related effect.

In the younger GLP conform 28-day range-finding study in rats a NOAEL of 100 mg/kg bw/day was established (NOTOX 2009). The study was started with doses of 0, 100 and 500 mg/kg bw/day. Due to severe signs of toxicity (strong body weight loss and clinical signs), the treatment for the high dosed animals was stopped after 9 days for 5 days of recovery and then they subsequently received 250 mg/kg bw/day for 28 days. Body weights were not affected at the end of the study. At the dose level of 250/500 mg/kg bw/day effects in hematology (increased prothrombin time (PT), lower reticulocyte and platelet counts) and clinical chemistry (higher alanine aminotransferase activity, higher inorganic phosphate levels) were seen. Additionally, a greenish discolouration of the kidneys among all animals, along with red-brown discolouration of the liver among most females and changes in histopathology such as hypertrophy of hepatocytes was evident. Absolute liver weights were increased by 25 and 45% at the high dose group for males and females, respectively. It is not clear whether the observed effects were caused by the initial 500 mg/kg bw/day treatment or by the later treatment with 250 mg/kg bw/ day.

4.11.4 Summary and discussion of reproductive toxicity

In a one-generation study according to OECD guideline 415 and GLP requirements, rats received doses of 30, 100 or 300 mg/kg bw/d per gavage (BASF SE 2011). Parental male and female rats were treated for a period of 110 and 126 days, respectively. The NOAEL (no observed adverse effect level) for fertility was the highest tested dose of 300 mg/kg bw/d. The 28-day toxicity studies in rats did not cause adverse effects to reproductive organs. Therefore, untoward alteration of fertility is considered to be unlikely.

The NOAEL for general, systemic toxicity of the test substance was 100 mg/kg bw/d for males and females based on the strong increase in liver weight accompanied by histopathology changes and for females only reduced food consumption and body weight gain at 300 mg/kg bw. In the range-finding study with males and non-pregnant females, a higher dose level of 500 mg/kg bw resulted in body weight loss and clinical signs, and dosing was aborted after only 9 days. The lower dose of 250 mg/kg bw was tolerated during the 28-day treatment period.

The NOAEL for developmental toxicity in the F1 progeny of the test substance treated groups was determined at 100 mg/kg bw/d, based on **reduced live birth index, pup mortality and reduced pup weights** at the next higher dose level of 300 mg/kg bw. The live birth index was reduced to 94% which is slightly below the historical range of 95-100%. The viability index was reduced to 86% compared to the historical range of 94-100%. High dose group pups were born with a lower body weight and although they showed normal body weight gain during lactation and the lactation index was not affected, the average pup body weight of 36.9g was still below the historical range of 41.3 – 53.7g at the end of lactation. Other adverse findings were not noted until and including scheduled necropsy. From the available information, there is no indication that the substance causes teratogenic effects; however this endpoint can only be completely assessed in a developmental/ teratogenicity study following OECD guideline 414.

Adverse effects on the offspring were observed at a dose that elucidated maternal toxicity. It is acknowledged that the development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms.

Parental toxicity was most clearly seen in changes in body weight gain. The offspring responded partially with inability to survive and reduced body weights. In the high-dose female population, the dams with total litter loss and /or small litter size (n=6) also revealed body weight gain below the group mean value during the gestation period, whereas the remaining females were rather unaffected. Furthermore, the group mean body weight gain value is in excess of the MTD and is by far exceeded for individual affected animals.

4.11.5 Comparison with criteria

According to the Guidance to Regulation (EC) No 1272/2008 on classification, labeling and packaging (CLP), toxicity to reproduction is split into adverse effects on sexual function and fertility and adverse effects on development of the offspring.

The one-generation study (OECD 415) showed no effects that would be indicative of adverse effects on sexual function and fertility. No alterations to male and female reproductive system, reproductive cycle normality, sexual behavior, fertility and parturition were noted. Other parameters mentioned in the CLP directive, such as premature reproductive senescence, cannot be routinely detected in the one-generation study. Overall, none of the hazard criteria regarding sexual function and fertility were fulfilled.

The one-generation study (OECD 415) showed adverse effects on development of the offspring. These are broadly defined in the CLP directive as ”any effect that interferes with the normal development of the conceptus, either before or after birth, resulting from exposure of either parent prior to conception, or exposure of the offspring during prenatal development, or postnatally, to the time of sexual maturation.”
The major manifestations of developmental toxicity as listed in EC regulation 1272/2008 include death of the developing organism, structural abnormality, altered growth and functional deficiency.
Reduced live birth index, pup mortality and reduced pup weights observed at the high dose group are indicative of developmental toxicity

In the absence of evidence from humans, the hazard category 1A is not applicable.

Category 1B (presumed human reproductive toxicant) has to be selected if “…such data…provide clear evidence of an adverse effect 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”.
In this study, pups of the highest dose groups were born with a lower body weight which is related to the slightly reduced ability to survive parturition and the first four days after birth. Parental animals of this dose group suffered from adverse effects so that the first criterium for assigning category 1B is not fulfilled. The second criterium is that the effect must not be secondary to a non-specific consequence of other toxic effects. Dams of the high dose group suffered from liver toxicity as verified by histopathology. An adaptive stress reaction was observed for the adrenal glands and body weight and food consumption were affected. Studies of much shorter duration showed that whereas low doses result in an adaptive liver enlargement, higher doses turn adverse and cause body weight loss at only slightly higher doses. All of the above is considered insufficient evidence that the developmental toxicity occurs independently of maternal toxicity and Category 1B is not appropriate.

Category 2 (suspected human reproductive toxicant) "is to be used if…such data…provide some evidence of an adverse effect 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 and where the evidence is not sufficiently convincing to place the substance in category 1".

Therefore, assignment of Category 2 is considered appropriate.

4.11.6 Conclusions on classification and labelling

Therefore, it is proposed to classify and label the substance for developmental toxicity as **Repr. 2 H361d** under CLP Regulation (EC) No. 1272/2008.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Sexual function and fertility

In a GLP-compliant one-generation study according to OECD test guideline (TG) 415 (BASF SE, 2011), 20 rats/sex/group were given 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone by gavage at dose levels of 0 (vehicle (propylene glycol) only), 30, 100, or 300 mg/kg bw/day. Reproductive indices were not affected, and in females no treatment-related effects were found on reproductive organs. In males in the high dose group, an absolute and relative testes weight increase was observed (107% and 113%, respectively), as well as an absolute and relative prostate weight decrease (80% and 85%, respectively) and an absolute, but not relative, seminal vesicles weight decrease (87%). However, no correlation to histopathology was observed for these weight changes.

The CLH report further refers to three subacute oral toxicity studies in rats (all by gavage) in which some parameters related to fertility were investigated. In a 14-day range-finding study with 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone at dose levels ranging from 100-3000 mg/kg bw/day, the gonad weights were not affected (Hazleton, 1989a). In the subsequent main study of 28-day duration, dose levels ranging from 10-500 mg/kg bw/day did not reveal macroscopic findings on reproductive organs, and therefore their weights were not determined and histopathology was not performed (Hazleton, 1989). In a 28-day range-finding study to the one-generation study, with dose levels of 100 and 500/250 mg/kg bw/day (500 mg/kg bw were not tolerated by the rats and reduced to 250 mg/kg bw after 9 days), no treatment-related effects were observed on histopathology of testes and epididymides, sperm motility and spermatogenesis (NOTOX, 2009).

In the absence of adverse effects observed on sexual function and fertility, the DS concluded that no classification for this endpoint is warranted.

Developmental toxicity

The one-generation study was also used to evaluate the occurrence of developmental effects. Mid- and high-dose females (100 and 300 mg/kg bw/day) had a significantly increased number of stillborn pups (that was still within historical control range at the mid dose). At the high dose only, a decreased live birth index was seen in females indicating an adverse effect of the test compound on reproductive performance at this dose level. Pup mortality was statistically significantly increased and pup body weights were statistically significantly reduced in the high-dose group (300 mg/kg bw/day). The respective findings were seen at doses where the dams prenatally and postnatally showed a reduction of body weight (in one dam) or body weight gain, and/or their food intake was affected. Other maternal effects reported in the mid and high dose groups were enlargement of the liver and adrenal glands, green/brown discoloration of the liver and kidneys, and red discoloration of the glandular stomach. These effects increased in a dose-dependent manner, with additional histopathology findings in liver and adrenal glands at the high dose only. According to the DS, the findings of systemic toxicity observed in the one-generation study were consistent with those of the subacute studies. These studies show that 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone causes a strong increase in liver weight up to a certain dose level. If that dose level is exceeded, the most prominent effect quickly becomes reduced food consumption and body weight loss. The actual dose level of this threshold appears to be influenced by vehicle and/or rat strain. Whereas the dose level of 500 mg/kg bw was tolerated without effects on body weight in one 28-day study with Sprague-Dawley rats and CMC as vehicle (Hazleton, 1989), it resulted in a strong decrease in food consumption and body weight loss within 9 days of dosing in another 28-day study with Wistar rats and propylene glycol as vehicle (NOTOX, 2009).

The DS concluded that pups of the high dose group were born with a lower body weight that was related to a slightly reduced ability to survive parturition and the first four days after birth, and that these effects were observed in dams suffering from liver toxicity and (adaptive) stress. According to the DS there is insufficient evidence that the developmental toxicity occurs independently of maternal toxicity. Therefore, the DS proposed 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone to be classified as Repr. 2 for developmental toxicity.

Comments received during public consultation

One manufacturer and two MSCAs agreed with classification in Category 2 for developmental toxicity. One MSCA questioned the involvement of maternal toxicity in the increase in stillborn pups, as the corrected maternal body weight cannot be calculated due to the lack of uterine and foetal weights. In particular, the MSCA they asked whether there was a link between liver toxicity and pup mortality for individual dams. The DS explained that there was no obvious trend, and this was also difficult to determine as there was no extreme variability in either pup mortality or histopathological findings.

Assessment and comparison with the classification criteria

Sexual function and fertility

RAC agrees with the DS that classification for fertility is not warranted, given that the only relevant findings, i.e. changes in the weights of male reproductive organs in the one-

generation study, were relatively small and not accompanied by histopathological or functional changes.

Developmental toxicity

An increase in both pre- and postnatal pup mortality as well as a decrease in pup weight were observed in the one-generation study (see for relevant results Tables 1 and 2).

Table 1: Female delivery data and pup mortality

	Historical data	**0 mg/kg bw/day**	**30 mg/kg bw/day**	**100 mg/kg bw/day**	**300 mg/kg bw/day**
Number of litters		18	19	17	17
Total number of pups		194	190	190	162
Pups delivered per dam (mean)	9.3-12.8	10.8	10.1	11.2	9.5
Females with stillborn pups, (N (%))		0 (0)	1 (5.3)	5 (29)*	8 (47)*
Stillborn pups, (N (%))	(0-4.5)	0 (0)	2 (1.0)	6 (3.2)*	9 (5.6)*
Live birth index (%)	95-100	100	99	97	94
Pups dead day 0 (N (%))		0 (0)	1 (0.5)	0 (0)	4 (2.6)
Pups dead day 1-4 (N (%))		0 (0)	3 (1.6)	3 (1.6)	18 (12)*
Pups dead day 5-21 (N (%))		0 (0)	0 (0)	1 (0.5)	1 (0.7)
Pups surviving days 0 to 4 (viability index; N (%))	(94-100)	194 (100)	185 (98)	181 (98)	131* (86)
Pups surviving days 4 to 21 (Lactation index; N (%))	(94-100)	134 (100)	139 (100)	129 (99)	103 (99)

*p<=0.05

Table 2: Overview of pup weight and maternal body weight

	Historical data	**0 mg/kg bw/day**	**30 mg/kg bw/day**	**100 mg/kg bw/day**	**300 mg/kg bw/day**
Pups delivered per dam (mean)	9.3-12.8	10.8	10.1	11.2	9.5
Live pups/litter day 1	9.3-12.8	10.8	9.8	10.7	7.8
Mean pup weight day 1 (g)	5.8 – 6.9	6.3	6.3	5.9	5.5*
Mean pup weight day 21 (g)	41.3 – 53.7	46.6	46.3	44.3	36.9*
Maternal bw gestation day 0 (g)		218.10	217.80	224.90	209.20
Maternal bw gestation day 20 (g)		315.80	311.70	314.50	292.7*
Maternal bw lactation day 0 (g)		248.8	246.4	252.4	232.0*
Maternal bw lactation day 21 (g)	226.7 – 307.7	273	274.5	278.6	260.3*
Maternal bw gain during gestation (g)		97.7	93.9	89.6	83.5
Maternal bw gain during lactation (g)		24.2	28.1	26.3	28.3

*p<=0.05

As can be seen from Table 1, both the number of stillborn pups and the number of females with stillborn pups were significantly increased in the mid- and high dose groups. However, at the mid dose, this increase was within the historical control range. Post-natal pup mortality was increased in the high dose group during the first four days, but not between PND 5-21. It should be noted that the pups were culled on day 4 to reach a maximum of 8 pups/litter, which may have reduced pup mortality after day 4.

Pup weight was significantly reduced in the high dose group only (Table 2). In this group, the absolute weight of brain, thymus, and spleen were reduced to 95, 73, and 70% of the weights of the control group respectively. The relative weights were 121, 90, and 87%, which indicates that the weight reduction of these organs was at least partly secondary to the general weight reduction of the pups in the high dose group.

RAC agrees with the DS that the increase in pup mortality and decrease in pup weight should be considered treatment-related effects on development. The DS however only considered the high dose effects relevant for classification, arguing that the increase in stillborn pups at the mid dose level was within the historical control range, just like the reduced livebirth index that was probably due to the relatively large litter size at this dose level. RAC disagrees with this assessment as the number of stillborn pups shows a clear dose-response relationship and the difference at the mid dose group was significant as compared to the concurrent control group, which has preference over historical control data. Stillbirth also occurred in multiple dams, which makes it less likely to be incidental. Besides, the litter size at the mid dose was only a bit larger than that of controls (11.2 vs 10.8) and well within historical control range. Further, also the average weight of the pups was reduced in the mid dose group, albeit not statistically significantly.

The main reason for the DS to propose a classification in Category 2 instead of 1B was the presence of maternal toxicity, consisting mainly of liver toxicity, (adaptive) stress reaction, and reductions in body weight/body weight gain and food consumption, some of which may have contributed to the developmental effects. This warrants a closer look at the maternal effects observed in the one-generation study.

Maternal body weight / body weight gain / food consumption

The maternal body weight gain of the high dose group was ~15% lower compared to the controls at the end of the gestation period. As can be seen from Table 18a in the CLH report, the lowest body weight gain was observed in four dams with small litters (not counting three dams that were not pregnant). There was no clear link between body weight gain of the individual dams and the number of stillborn pups. In the absence of information on corrected maternal body weights (no data on uterine and foetal weights available), it cannot be determined whether the reduction in maternal body weight was secondary to the developmental effects or the developmental effects are secondary to the reduced maternal body weights.

The mean difference in body weight between high dose animals and controls was 4% at gestation day 0 and increased to 7% at gestation day 20. During lactation, the body weight of the high dose group was 5-8% lower than of the control group, without a clear trend in time.

No signification changes in body weight or body weight gain were noted in the exposed males, nor in the females during the premating period. For the mid dose group, where a small increase in stillbirth was observed, no statistically significant effects on maternal body weight or body weight gain during gestation and lactation was noted (body weight gain was reduced, in the same order of magnitude as the reduced pup weights at the mid dose).

In a 28-day range-finding study to the one-generation study (NOTOX, 2009) marked body weight loss was seen at 500 mg/kg bw/day, but not at 250 mg/kg bw/day, which is only slightly below the high dose of 300 mg/kg bw/day in the one-generation study. Another 28-day study, in another rat strain and with another vehicle (Hazleton 1989), reported no decrease in body weight at 500 mg/kg bw/day.

Food consumption was only affected during the lactation period, and only in high dose females (up to 20% lower food consumption as compared to controls).

Studies that evaluated the effect of maternal feed restriction on reproductive parameters found no effect of maternal body weight on the occurrence of stillborn pups or on pup viability (Carney *et al.* 2004, Chernoff *et al.* 2009). However, a decrease in body weight of the pups was observed at 30% and 50% feed reduction, corresponding to a maternal body weight reduction of 10-20% and 17-32% respectively. The body weight reduction in pups was 10-20% at 30% feed restriction and 12-47% at 50% feed restriction. It should be noted that the body weight reduction in the dams in the one-generation study was at most 8% during gestation and lactation, which is less than the level at which a reduction in pup weight was reported in the feed restriction studies. Additionally, the reduction in pup weight during lactation was 13-24% in the high dose group, which is more than can be adequately explained by the reduction in maternal body weight of 5-8% in the same period.

Based on these considerations, it is the opinion of RAC that the reductions in maternal body weight, body weight gain, and food consumption were at least partly caused by the smaller litters and increased pup mortality in the high dose group. It is considered unlikely that the observed increase in stillborn pups and postnatal mortality was secondary to these maternal effects.

Maternal histopathological effects

Other maternal effects in the one-generation study consisted of gross lesions (discolorations) in the liver, kidneys, and glandular stomach (see Tables 23-25 in the CLH report) at both the mid and high dose. The dose-dependent discoloration of the kidneys was without histopathological correlate. The red focal discolorations in the glandular stomach correlated with mucosal hyperemia, most likely caused by local irritation. They occurred in 5/20 mid dose dams and in 3/20 high dose dams (so not dose-related), but also in 2/20 control dams. The findings were only of minimal to slight severity, and they were considered adaptive by the DS. RAC noted that in males the glandular stomach findings showed a dose-response relationship and were more pronounced than in females, without however affecting body weight or food consumption. RAC considered it very unlikely that the slight irritative effect in females has caused the developmental effects (in particular the pre-natal and postnatal mortality), also noting that at the high dose only 3 dams had this effect, whereas 8 dams had stillborn pups.

The absolute and relative liver weights were increased in a dose-related fashion in the mid 114 and 112%, respectively) and high dose females (144 and 150%, respectively), with histopathological correlate in the high dose only. Given the magnitude of the effect, RAC considered the increases in liver weight in the high dose females to be adverse, but noted that the histopathological findings in this group were limited to minimal to slight hepatocellular hypertrophy only. Hence, the enlargement of the liver is likely an adaptive response rather than true liver toxicity. According to the DS there is no clear link between liver toxicity and pup mortality for the individual dams.

The absolute and relative adrenal weights were also dose-relatedly increased in the mid and high dose females, again with a histopathological correlate in the high dose only, consisting of cortical cells with condensed eosinophilic cytoplasm devoid of lipid vacuoles in the zona fasciculata. The DS suggested that this effect may represent an ACTH-induced depletion related to stress and therefore a secondary, adaptive effect.

Conclusion

2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone caused developmental effects in a one-generation study in rats. These consisted of increases in the number of stillborn pups (statistically significant and dose-related at the mid and high dose, but outside the historical control range only for the high dose) and in postnatal mortality (statistically significant, at the high dose), and in decreases in pup body weight (dose-related at the mid and high dose, but statistically significant only at the high dose). These are considered severe effects, in particular the first two which, when combined, indicate a rather strong effect (approximately 20% mortality at the high dose). At the high dose the developmental effects were observed in the presence of several maternal effects.

In the absence of evidence in humans, category 1A is not applicable.

Given that the developmental effects were observed in the presence of other toxic effects, classification may not be appropriate if the developmental effects can be considered as secondary non-specific consequence of these other toxic effects. When looking individually at the maternal effects at the high dose, neither the reduction in maternal body weight (gain) nor the liver toxicity are likely to be directly causative for the developmental effects observed given their relatively small magnitude and nature. It was suggested that some non-specific mechanisms related to stress in the dams may have played a role at the high dose. RAC however noted that no stress or other significant maternal effects were observed at the mid dose, whereas developmental effects were also observed at that dose in a dose-related way. RAC therefore considers the developmental effects observed not to be a secondary non-specific consequence of maternal toxicity, and classification in either category 1B or 2 is warranted. According to the criteria, category 2 could be more appropriate than category 1B if the quality of the study makes the evidence less convincing. That, however, is not the case here, as the one-generation study in which the effects were seen is of good quality study. Looking further at the severity of the effects observed, RAC considers in particular stillbirth and postnatal mortality to be severe effects, relevant for humans. Given additionally the statistical significance of these effects and the dose-response relation found for stillbirth, classification in category 1B is considered more appropriate than category 2. Hence, RAC recommends 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone to be classified as **Repr. 1B (H360D; May damage the unborn child)**.

4.12 Other effects

Not relevant for this harmonised classification and labelling proposal

5 ENVIRONMENTAL HAZARD ASSESSMENT

In the time period between the introduction of the legal classification for acute and long term aquatic toxicity and the first submission of this CLH-dossier in December 2014 no new experimental data relating to the environmental was finalized.

6 OTHER INFORMATION

Not relevant for this dossier.

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