Agency technical report on the classification and labelling of: acetophenone

EC Number: 202-708-7
CAS Number: 98-86-2

September 2025

Contents

Brief summary

The conclusion of the Agency technical report is that acetophenone meets the classification criteria for:

STOT SE 3; H336 (May cause drowsiness or dizziness)

Repr. 1B; H360FD (May damage fertility. May damage the unborn child)

Not classified for acute oral toxicity.

Is this in agreement with the RAC opinion? YES

At the time of publication, this mandatory classification and labelling (MCL) has not been agreed and/or adopted in Great Britain.

This is a targeted technical report which only considers acute toxicity via the oral route, specific target organ toxicity – single exposure (STOT SE), and reproductive toxicity. These were the only hazard classes considered in the EU Committee for Risk Assessment (RAC) Opinion.

This substance has an existing MCL which includes Eye Irrit. 2. Eye irritation is not assessed in this technical report, therefore Eye Irrit. 2 should be retained in the GB MCL list.

Introduction

Under Article 37 of the GB CLP Regulation[1], the Agency[2] is required to produce a technical report for each substance on which the Committee for Risk Assessment (RAC) of the European Chemicals Agency produces an opinion[3].

This technical report documents an independent scientific assessment, conducted by HSE technical specialists, of the classification and labelling of acetophenone.

Table 1. Information considered in the scientific assessment

Document	**Included in assessment**
EU CLH report	Yes
Annexes to the EU CLH report	Not applicable
RAC opinion	Yes
Background document	Yes
Information submitted during the EU public consultation process (RCOM table, including attachments)	Yes
RAC minority opinion(s)	Not applicable
Other information:	No

This information has been evaluated against the classification and labelling criteria set out in the GB CLP Regulation.

[1]The retained CLP Regulation (EU) No. 1272/2008 as amended for Great Britain

[2] HSE acting in its capacity as the GB CLP Agency

[3] Under Article 37(4) of Regulation (EU) No 1272/2008 on classification, labelling and packaging of substances and mixtures

Overview of current and proposed classification and labelling

Table 2. Current and proposed classification and labelling

	Index No.	International Chemical Identification	EC No.	CAS No.	Classification		Labelling			Specific Concentration Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard Statement Code(s)	Suppl. Hazard Statement Code(s)		
GB MCL List entry	606-042-00-1	acetophenone	202-708-7	98-86-2	Acute Tox. 4* Eye Irrit. 2	H302 H319	GHS07 Wng	H302 H319			
EU dossier submitter's proposal	606-042-00-1	acetophenone	202-708-7	98-86-2	**Add** Repr. 1B STOT SE 3 **Remove** Acute Tox. 4*	**Add** H360FD H336 **Remove** H302	**Add** GHS08 **Modify** Dgr	**Add** H360FD H336 **Remove** H302			
EU RAC opinion	606-042-00-1	acetophenone	202-708-7	98-86-2	**Add** Repr. 1B STOT SE 3 **Remove** Acute Tox. 4*	**Add** H360FD H336 **Remove** H302	**Add** GHS08 **Modify** Dgr	**Add** H360FD H336 **Remove** H302			
Agency technical report conclusion	606-042-00-1	acetophenone	202-708-7	98-86-2	**Add** Repr. 1B STOT SE 3 **Remove** Acute Tox. 4*	**Add** H360FD H336 **Remove** H302	**Add** GHS08 **Modify** Dgr	**Add** H360FD H336 **Remove** H302			
Resulting MCL entry	606-042-00-1	acetophenone	202-708-7	98-86-2	Repr. 1B STOT SE 3 Eye Irrit. 2	H360FD H336 H319	GHS08 GHS07 Dgr	H360FD H336 H319			

Background

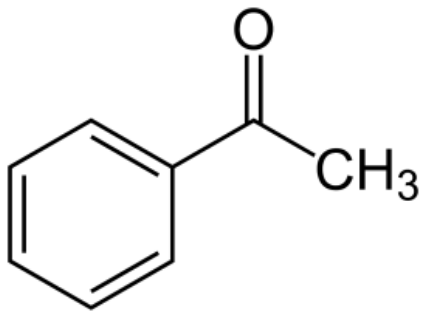
Active substance in Plant Protection Products: ☐

Active substance in Biocidal Products: ☐

Chemical registered under REACH: ☒

Acetophenone, a colourless liquid that forms laminar crystals at lower temperatures, is used as a cleaning agent, solvent and in polymer manufacturing and processing at industrial sites (ECHA, 2025; CLH, 2023). It is also used by professional workers and consumers in air care products, fillers, putties, plasters, modelling clay, cleaning and care products, lubricants, greases, release products, coatings and paints, thinners, paint removers and finger paints (CLH, 2023). Acetophenone has been previously used in medicine as an aesthetic and hypnotic agent, under the name Hypnone (CLH, 2023).

Figure 1: Structure of acetophenone (taken from page 1 of the CLH report (CLH, 2023))



The dossier submitter (DS; Spain) prepared the CLH report to address concerns for effects on reproductive toxicity, in accordance with Article 36 (1)(d) of the CLP Regulation, and to revise the existing minimum Acute Tox 4* classification.

Scientific assessment of the physical, human health and environmental hazard classes

Physical Hazards

Classification agreed by RAC:

Not assessed in the CLH report or RAC opinion.

Health Hazards

Acute Toxicity

Classification agreed by RAC:

Acute toxicity – oral route

Six non-GLP acute oral toxicity studies in rats were available to RAC, but only two were used for the assessment of the acute oral toxicity of acetophenone, owing to their reliability ratings.

In the key study, conducted according to a similar method to OECD TG 401, Sprague Dawley (SD) rats (5/sex/group) were administered a single dose of acetophenone (purity not specified) via oral gavage (Anonymous, 1981). The dose levels were 0, 1030, 1648, 2575, and 4120 mg/kg bw. Mortalities were reported within 24 hours post administration at 1030 mg/kg bw (1 male, 1 female), at 1648 mg/kg bw (2 males, 1 female), 2572 mg/kg bw (2 males, 4 females), and 4120 mg/kg bw (5 males, 5 females). The DS noted that there were unspecific clinical signs, and that deceased animals showed liver hyperaemia. The LD_{50} was determined to be 2081 mg/kg bw.

The supportive study was also conducted according to a method similar to OECD TG 401. SD rats were administered a single dose of acetophenone (99.7% purity) via oral gavage, at dose levels of 0, 710, 1400, 2000, 2800, 3900 mg/kg bw (Anonymous, 1978). Three out of ten rats died at 2000 mg/kg bw within 48 hours after administration of acetophenone, while all rats died at 2800 and 3900 mg/kg bw within 24 hours post administration. Within 15 minutes post administration, staggering gait followed by inhibition of turn-around reflex,

watery eyes, palpebral ptosis and slowed down breath were observed at all doses. The LD_{50} was determined to be 2200 mg/kg bw.

RAC noted that the above studies (Anonymous, 1981; Anonymous 1978) were not available to the Technical Committee on Classification and Labelling (TC C&L) at the time of the previous classification assessment of acetophenone. Both studies gave LD_{50} values above the upper guidance value of 2000 mg/kg bw for classification in Category 4 for acute oral toxicity. The other four available studies, on which RAC noted the current EU harmonised classification is based, gave LD_{50} values of 3200 mg/kg bw (Jenner *et al*., 1964), 900 mg/kg bw (Smith and Carpenter, 1948), 740 mg/kg/ bw (Tiunov *et al*., 1986), and 3000 mg/kg bw (Smith and Carpenter, 1944). However, RAC concluded that the reliability of these values could not be assessed, and therefore the studies could not be considered in the assessment of acetophenone's acute oral toxicity.

As the lowest LD_{50} in the key and supportive studies was 2081 mg/kg (Anonymous, 1981), RAC agreed with the DS that the classification criteria for acute oral toxicity were not met and the existing classification of acetophenone as Acute Tox. 4*; H302 should be removed.

Acute toxicity – dermal route

Not assessed in the CLH dossier or RAC opinion.

Acute toxicity – inhalation route

Not assessed in the CLH dossier or RAC opinion.

Classification proposed by the Agency:

Acute toxicity – oral route

The Agency agrees with RAC's conclusion on classification. Acetophenone does not meet the classification criteria for acute toxicity. The current classification of Acute Tox. 4*; H302 should be removed.

Specific target organ toxicity – single exposure (STOT SE)

Classification agreed by RAC:

RAC referred to the studies on acute oral toxicity (see Acute toxicity section in this report), as well as one acute dermal toxicity study, in their assessment of STOT SE. In both acute oral toxicity studies, narcotic effects were observed from the lowest dose, in the form of

decreased mobility and staggering gait from 1030 mg/kg bw (Anonymous, 1981), staggering gait and inhibition of turn-around reflex from 15 minutes to 48 hours after administration of 710 mg/kg bw (Anonymous, 1978), and reduced spontaneous activity, flabby appearance and prostration at dose levels > 710 mg/kg bw (Anonymous, 1978).

In a dermal acute toxicity study conducted by Anonymous 1978 (similar to OECD TG 402; non-GLP), SD rats (5/sex/group) received single dermal occlusive applications of acetophenone (purity 99.7%) at dose levels of 0, 1820, 2360, 3000, 4000 and 5200 mg/kg bw/d for 24 hours. Transient clinical symptoms were observed for up to 48 hours, consisting of reduced spontaneous activity and palpebral ptosis at all doses from 1-6 hours after administration, and staggering gait was observed from 2360 mg/kg bw in all animals up to 48 hours.

Five repeated dose toxicity studies were also considered by RAC in their STOT SE assessment, including one subchronic toxicity study (OECD TG 408, GLP, Anonymous 2016b), one combined repeated dose toxicity study with reproductive/developmental toxicity screening test (OECD TG 422, GLP, Kapp *et al.,* 2003), an extended one-generation reproductive toxicity study (EOGRTS) with developmental neurotoxicity (DNT) cohort (OECD TG 443, GLP, Anonymous 2021) and two prenatal developmental toxicity studies (PNDT) (OECD TG 414, GLP, Anonymous 2016a; Anonymous 2020).

In the subchronic study, Wistar rats (10/sex/group) were administered acetophenone in corn oil at doses of 0, 125, 250 and 500 mg/kg bw/d by oral gavage for 90 days (Anonymous, 2016b). At 500 mg/kg bw/d, a slight to moderate reduction in spontaneous activity was observed in all male rats and most females on almost all days of treatment. Transient ataxia was also observed in some males and one female on a few days in the first week.

In the combined repeated dose study with reproduction/developmental toxicity screening test, SD rats (10 males, 5 females per dose group in the short-term repeated dose part) were administered acetophenone via oral gavage at doses of 0, 75, 225, and 750 mg/kg bw/d from 14 days before mating to lactation day 3 (Kapp *et al.,* 2003). In this study, wobbly gait was observed at 750 mg/kg bw post-dosing in all rats but not pre-dosing throughout the treatment period.

In the EOGRTS with DNT cohort, SD rats were administered acetophenone via the drinking water at dose levels of 0, 75, 225, and 500 mg/kg bw/d. Group sizes were 24, 20-21 and 10/sex in the P0, C1 and C2 cohorts, respectively. Male and female rats in the parental generation (P0) and all cohorts at 225 mg/kg bw/d and above showed transient reduced spontaneous activity and half closed eyes. At 500 mg/kg bw post-dosing, wobbly gait was also reported for the males in the P0 generation, and in males and females in the C1A and C2A cohorts. RAC noted that these effects were all observed after treatment but not before dosing.

In the rat PNDT, female Wistar rats (35 in ctrl and high dose, and 25 in low and mid dose groups), were administered acetophenone via oral gavage at dose levels of 0, 125, 300 and 750 mg/kg bw/d from gestation day (GD) 5 to 19 (Anonymous, 2016a). The study author reported transient reductions in spontaneous activity in three single female rats on 1-2 days of treatment at the mid dose. At 750 mg/kg bw/d slightly to severely reduced spontaneous activity was also reported in most females post-dosing on several days of treatment. In several cases, this was associated with half eyelid closure, prone position and ataxia.

In the rabbit PNDT, female New Zealand White (NZW) rabbits (22/group) were administered acetophenone at doses of 0, 60, 170 and 500 mg/kg bw/d via oral gavage from GD 6 to 28 (Anonymous, 2020). All rabbits showed decreased activity and/or wobbly gait 1 hour after dosing at 500 mg/kg bw, from GD 6 to GD 27, and were reported to recover within the day. Additionally, two single females were reported to have subdued behaviour on GD 9 with laboured and shallow breathing after 1–2 hour post dosing, recovering within the day.

While there were no human data presented in the CLH report or registration dossier, RAC acknowledged old publications from the nineteenth century, which are not publicly available, reporting the use of acetophenone as a hypnotic and sedative agent in human medicine. Additionally, the US EPA has also reported the use of acetophenone as an anticonvulsant and hypnotic agent (US EPA, 2011).

RAC Conclusion

Based on the transient effects such as lethargy, decreased activity and wobbly gait, that were observed after oral gavage administration in the animal studies and considering the previous use of acetophenone as a hypnotic agent, RAC concluded that classification of acetophenone as STOT SE 3; H336 (May cause drowsiness or dizziness) was warranted.

Classification proposed by the Agency:

The Agency agrees with RAC's conclusion on classification. Acetophenone meets the criteria for classification with **STOT SE 3; H336 (May cause drowsiness or dizziness)**.

Skin corrosion/irritation

Not assessed in the CLH dossier or RAC opinion.

Serious eye damage/irritation

Not assessed in the CLH dossier or RAC opinion.

Respiratory sensitisation

Not assessed in the CLH dossier or RAC opinion.

Skin sensitisation

Not assessed in the CLH dossier or RAC opinion.

Specific target organ toxicity – repeated exposure (STOT RE)

Not assessed in the CLH dossier or RAC opinion.

Germ cell mutagenicity

Not assessed in the CLH dossier or RAC opinion.

Carcinogenicity

Not assessed in the CLH dossier or RAC opinion.

Reproductive toxicity

Adverse effects on sexual function and fertility

RAC's assessment of sexual function and fertility was based on one EOGRTS with DNT cohort (OECD TG 443, GLP, Anonymous 2021) and one combined repeated dose toxicity study with reproduction/developmental toxicity screening test (OECD TG 422, GLP, Kapp *et al.*, 2003). Both studies were carried out in SD rats, and the test substance was administered via oral gavage.

Extended-one generation reproductive toxicity study (Anonymous, 2021)

In this OECD TG 443 study, SD rats (24/sex/dose) were administered acetophenone at doses of 0, 75, 225 and 500 mg/kg bw/d from 10 weeks before mating, through mating, gestation, and lactation until pup (F1) weaning. At weaning, F1 pups were assigned to cohorts C1A and C1B for reproductive and developmental testing, and C2A and C2B for developmental neurotoxicity testing.

Transient hypoactivity and/or half-closed eyes consistent with the narcotic effects of acetophenone were observed in both P0 males and females post-dosing from 225 mg/kg bw/d. At 500 mg/kg bw/d, these effects were observed alongside loud/abdominal breathing, staggering gait, continuous chewing, and/or ventral recumbency in some animals. In the treated groups, a greater number of individuals showed ptyalism and/or burrowing activity compared to controls. These findings were considered treatment-related but not adverse since they are commonly observed after a gavage procedure with irritant substance. Other P0 systemic effects were considered by RAC to be adaptive or non-adverse owing to their low severity and/or nature; these consisted of: increased liver weights in the mid and high-dose groups (absolute/relative increases of 17/24% and 31/40% for mid and high-dose males, and 15/12% and 17/16% for mid and high-dose females, respectively); minimal to moderate dose related tubular basophilia (4, 8, 10 and 20 in ctrl, low, mid and high dose) and accumulation of hyaline droplets (0, 2, 7 and 23 in the ctrl, low, mid and high dose) in males; slight hyperkeratosis in the forestomach and oesophagus of males and females in all treated groups; and brown pigment in the spleen in all treated groups (0/0, 3/2, 5/2 and 15/9 for M/F in ctrl, low, mid and high dose, respectively).

In high-dose P0 males, there were statistically significant decreases in mean body weight gain (-9%) over the whole treatment period and in mean terminal body weight (-6%) when compared to the control group. In the first week of treatment, all P0 males were observed to have a decrease in food consumption (-17%). The level of food consumption became comparable with the control group for the rest of the treatment duration.

High-dose P0 females showed increased body weight gain (10%) and overall increased mean body weight (4%) at the end of the premating period compared to controls, although this was not statistically significant. Female body weight was comparable to the control group during the gestation and lactation periods. Food consumption was decreased compared to the control in the first week of premating (-14%) and between LD 4-21 (-32%).

No mating was reported in one female at 225 mg/kg bw/d and in three females at 500mg/kg bw/d, resulting in a dose-dependent decrease in mating index (100%, 100%, 95.7% and 87.5% in the control, low, mid and high dose groups, respectively). RAC noted that the high-dose mating index was clearly outside of the historical control data (HCD) range of 95.8-100%. The calculation of the mating index excluded two females sacrificed from the control and mid-dose during the premating period on humane grounds. One

female in the low dose group and one in the mid dose group did not conceive and were both sacrificed.

RAC considered all premature sacrifices in P0 females to be associated with reproductive disorders, such as difficulty to deliver and/or total litter loss (Table 3).

Table 3: Mortality in P0 females (taken from page 10 of the RAC opinion, ECHA (2025))

Dose level (mg/kg bw/d)	**0**	**75**	**225**	**500**
Number of females	24	24	24	24
Sacrificed during premating	1	0	1	0
Sacrificed due to mating failure	0	0	**1**	**3**
Sacrificed since not pregnant	0	**1**	**1**	**0**
Sacrificed due to dystocia#	0	**3**	**1**	**3**
Sacrificed due to dead litter	0	**0**	**3**	**11**
Overall number sacrificed due to reproductive disorders	0	**4**	**6**	**17**

#Reported in the full study report (FSR) as dams sacrificed due to difficulties in delivery or dams pregnant/no delivery sacrificed at GD 25-26

There were no effects observed on the oestrous cycle, follicle and corpora lutea counts, mating period, fertility index, implantation sites, gestation length or gestation index. RAC considered the main critical effect on fertility to be dystocia, which was observed in 0/23 females in the control, 3/23 at the low dose, 1/21 at the mid dose, and 3/21 at the high dose. In these females, parturition either did not start or they suffered difficulties to deliver. RAC additionally noted that 3 and 11 dams at the mid and high dose, respectively, were sacrificed owing to total litter loss between postnatal day (PND) 1 and 4. They further discussed this effect under ‘Adverse effects on development’ but noted that 2 mid-dose and 4 high-dose females sacrificed as a result of total litter loss were found to have retained placenta and/or dead foetuses during necropsy, indicating incomplete parturition (see R21066, R021071, R21075, R21077, R21085 and R21095 in Table 4). A summary of the clinical observations and uterus macroscopic findings in P0 dams with reproductive disorders was provided by RAC:

Table 4: Clinical observations and uterus macroscopic findings in P0 dams with reproductive disorders (taken from page 12 of the RAC opinion; ECHA, 2025)

Dose level (mg/kg bw/d)	Animal ID	Day of sacrifice (treatment day)	Cause of death/ sacrifice	Narcotic-like effects from GD1 to sacrifice. Treatment days of occurrence (total number of days)			Macroscopic lesions in uterus at sacrifice
				Hypoactivity	Staggering gait	Half-closed eyes	
75	R21039	GD25 (100)	No delivery	(0)	(0)	(0)	3 scars, 4 foetuses
	R21040	GD24 (111)	Difficulty to deliver	(0)	(0)	(0)	10 placentas, 6 scars, 1 dead foetus
	R21041	GD23(99)	Difficulty to deliver	(0)	(0)	(0)	9 placentas,2 scars, 6 dead foetuses
225	R21054	GD24(97)	Difficulty to deliver	(0)	(0)	(0)	16 placentas, 2 scars, 1 dead foetus
	R21066	LD2 (101)	Dead litter	(0)	(0)	(0)	2 placentas
	R21068	LD2 (101)	Dead litter	(0)	(0)	(0)	_
	R21071	LD3 (101)	Dead litter	98-99 (2)	(0)	(0)	3 placentas, 1 late resorption
500	R21075	LD1 (98)	Dead litter	77-80, 95-96 (6)	(0)	79-80 (2)	2 placentas
	R21076	GD26 (99)	No delivery	79-80 (2)	(0)	92 (1)	1 dead foetus
	R21077	LD1 (96)	Dead litter	76, 79-81, 83 (5)	(0)	80, 92 (2)	2 placentas, 2 foetuses
	R21082	LD3 (104)	Dead litter	79-81, 97, 103 (4)	(0)	80-81, 92-93, 103 (5)	_

Dose level (mg/kg bw/d)	Animal ID	Day of sacrifice (treatment day)	Cause of death/ sacrifice	Narcotic-like effects from GD1 to sacrifice. Treatment days of occurrence (total number of days)			Macroscopic lesions in uterus at sacrifice
				Hypoactivity	Staggering gait	Half-closed eyes	
	R21084	GD25 (99)	Difficulty to deliver	77-81, 83, 85, 90, 97-98 (10)	(0)	79-85, 92, 97-98 (9)	5 placentas, 12 scars, 1 dead foetus
	R21085	LD1 (97)	Dead litter	79-80, 82-83 (4)	(0)	79-80, 92 (3)	1 placenta
	R21088	LD1 (98)	Dead litter	80, 82, 88-91, 97 (7)	(0)	80-82, 92, 97 (5)	_
	R21089	LD1 (98)	Dead litter	80-81, 84, 92, 95-97 (7)	(0)	80, 83, 88-91, 97 (7)	_
	R21090	LD2 (101)	Dead litter	80, 83, 88, 90-91 (5)	(0)	80, 84, 92, 98-99 (5)	_
	R21091	GD25 (103)	No delivery	80, 100-102 (4)	(0)	80, 92-94, 100 (5)	Placental remnants
	R21092	LD4 (103)	Dead litter	80, 82-83, 88-89, 100-101 (7)	88-89 (2)	80, 82-85, 92-93, 95-96, 100 (10)	_
	R21093	LD2 (109)	Dead litter	84-86, 88-89, 101-103, 105, 107-108 (11)	(0)	84, 92-99, 101-103 (12)	_
	R21095	LD3 (101)	Dead litter	79-80, 84-85, 97 (5)	(0)	80, 92, 99-100 (4)	8 placentas
	R21096	LD1 (99)	Dead litter	80, 89-91, 97-98 (6)	(0)	80, 82, 92-93, 97-98 (6)	_

GD: Gestation day; LD: Lactation day; _: no macroscopic findings

The DS concluded that the dystocia and decrease in the mating index were adverse effects on sexual function and fertility. F1 males in the high dose group were observed to have significant delay (+3 days) in their sexual maturation when compared with those in the control group. RAC noted that there was a decrease in mean body weight at weaning in this group compared to the control (-23%), but that the mean body weight at balano-preputial separation was comparable the control. Therefore, they considered that the delay in sexual maturation could be attributed to delayed general development. F1 females also showed a dose-related delay in sexual maturation in all dose groups, which reached statistical significance in the high dose group (+3.5 days compared to the control). Unlike the males, F1 females showed no significant body weight change at weaning compared to controls, and RAC noted that mean bodyweight at vaginal opening was slightly higher compared to the control group. On this basis, the delayed sexual maturation in F1 females were not considered by RAC to be a consequence of delayed post-natal growth.

Combined repeated dose toxicity study (Kapp et al., 2003)

In the OECD TG 422 study, SD rats (10 males and 10 females per dose group for the reproductive screening, plus 5 additional females for the repeated dose toxicity part of the test) were administered 0, 75, 225 and 750 mg/kg bw of acetophenone daily from 14 days before mating to LD 3.

From 225 mg/kg bw onwards, P0 males and females showed salivation, while staggering gait was observed in both sexes at 750 mg/kg bw. Urine stains were observed at all doses in P0 females, but only at 750 mg/kg bw for P0 males. Males in the high dose groups also showed reduced forelimb grip strength and motor activity.

Statistically significant body weight loss (-21g compared to +2g in control) and reduced food consumption (-41%) were observed in high-dose males during days 0-3 of the premating period. Females in the mid and high dose groups showed statistically significant decreases in food consumption (-13% and -44%, respectively), along with non-statistically significant body weight loss during days 0-3 prior to mating (-10g and -16g, respectively, compared to -3g in control). A further body weight reduction was observed in high-dose females during GD 0-7 (-39% compared to control) but was comparable to control values afterwards.

As in the OECD TG 443 study, all unscheduled sacrifices in this study were associated with reproductive disorders; these consisted of 3 females in the control group (1 failing to mate; 2 not pregnant), 1 female at the low dose (not pregnant) and 7 females at the high dose (1 failing to mate; 6 with total litter loss between LD 1-4).

One female showed prolonged parturition in the high-dose group. There were no other effects on fertility parameters.

RAC conclusion

RAC considered that the EOGRTS with DNT cohort conducted by Anonymous, 2021 showed clear evidence of adverse effects on sexual function and fertility. Exposure to acetophenone caused severe alteration in the parturition process including dystocia and incomplete delivery at all dose levels. In the combined study conducted by Kapp *et al.* (2003), delayed parturition was observed in one high-dose female.

All premature sacrifices in the OECD TG 443 EOGRTS (Anonymous, 2021) were associated with reproductive disorders. No mortality was linked to systemic toxicity and further analysis of individual data did not show any correlation between the narcotic effects caused by acetophenone and dystocia or incomplete delivery. RAC considered that the increased incidence of dams with dystocia and/or incomplete delivery were not secondary unspecific effects, as they occurred in the absence of general toxicity.

RAC acknowledged that while narcosis may transiently interfere with mating behaviour, no clear correlation between narcosis and mating failure could be identified based on analysis of individual data in the EOGRTS.

RAC considered that the delay in sexual maturity in F1 males in the EOGRTS may reflect delayed growth rather than a direct effect on sexual development. In contrast, RAC determined that the delay in puberty onset in high-dose F1 females in the same study was relevant for classification purposes.

As no human data were available, RAC agreed that the classification in Category 1A was not supported. Based on the evidence provided in the studies, RAC concluded that acetophenone warranted classification with **Repr. 1B; H360F (May damage fertility).**

<u>Adverse effects on development</u>

The assessment of developmental toxicity was based on four experimental studies: the EOGRTS with DNT cohort (OECD TG 443, GLP, Anonymous 2021), the combined reproductive/developmental study (OECD TG 422, GLP, Kapp et al., 2003), and two PNDTs (OECD TG 414, GLP, Anonymous 2016a; Anonymous 2020).

Extended-one generation reproductive toxicity study (Anonymous, 2021)

In the OECD TG 443 study, SD rats (24/sex/dose) were administered acetophenone at doses of 0, 75, 225 and 500 mg/kg bw/d (99.79%) via oral gavage from 10 weeks before mating, through mating, gestation and lactation until pup (F1) weaning. At weaning, F1 pups were assigned to cohorts C1A and C1B for reproductive and developmental testing, and C2A and C2B for developmental neurotoxicity testing. The first check of litter size,

number of live, dead and cannibalised pups, clinical examination and sexing of each pup occurred on PND 1.

At the mid and high dose, there was severe perinatal mortality (see 'Adverse effects on sexual function and fertility'). This resulted in insufficient numbers of surviving pups at 500 mg/kg bw. Consequently, the high dose group in C1A contained only 10 males, and there were only 5 animals/sex in the C2A high dose group and not enough pups for high-dose C1B and C2B groups.

Treated animals showed a dose-dependent increase in post-implantation loss, which reached statistical significance at the highest dose (29.8% compared to 16.1% loss in the control group; an 85% increase). This correlated with a dose-related decrease in the number of pups delivered: 284 in the control, 253 at low dose, 212 at mid dose, and 196 at high dose. RAC noted that there was a severe, statistically significant increase in the mean number of dead pups on PND 1 (either stillborn or died between birth and first check), represented by a mean of 6.7 dead pups per litter at PND 1 first check, compared to 0.4 in the control. Additionally, there was a statistically significant decrease in the number of females with total litter loss between PND 1 and PND 4 at the mid and high dose (3 females in the mid dose and 11 females in the high dose, respectively). Consequently, at the mid and high dose, there were decreases in the live birth index (calculated to be 79.6% and 34.1%, respectively, compared to 96.8% in the control) and viability index (calculated to be 77.7% and 38.1%, respectively, compared to 96.3% in the control).

Necropsy revealed that 23 out of 43 pups in the mid-dose and 79 out of 132 pups in the high dose were autolysed. Additionally, 12 out of 42 in the mid-dose and 34/132 in the high dose had no presence of milk in the stomach.

Table 5 below provides a summary of the delivery data and offspring survival across all treated groups and control group.

Table 5: Delivery data and offspring survival (taken from page 17-18 of the RAC opinion; ECHA, 2025)

Dose level (mg/kg bw/d)	0	75	225	500	HCD range
No of litters at PND1	23	20	20	18	-
No of litters with live pups at PND1	23	20	19	**10**	-
No of litters with live pups at PND4	23	20	**17**	**7**	-
No of litters with live pups at PND21	23	20	**17**	**7**	-
Number of females with total litter loss PND1-PND4	0	0	**3**	**11**	-

Dose level (mg/kg bw/d)		0	75	225	500	HCD range
No of implantations	Total	338	318	283	282	-
	Mean	14.7	15.9	14.1	15.7	14.7-16.4
No of pups delivered	Total	284	253	**212**	**196**	-
	Mean	12.3	12.7	**10.6**	**10.8**	12.3-13.9
Implantation loss	Mean %	16.1	20.3	**24.1**	**29.8***	11.5-16.3
	Compared to controls	-	+26%	**+50%**	**+85%**	-
No of live pups on PND1	Total	274	253	**167**	**75**	-
	Mean including all litters at PND1#	11.9	11.9	**8.4**	**4.2**	11.8-13.9
	Mean excluding total litter losses	11.9	11.9	**8.8****	**7.5****	-
Total		10	16	**45**	**121**	-
No of dead pups on PND1 (mean)		0.4	0.6	**2.3**	**6.7**	0.0-0.6
Live birth index	Mean %#	96.8	94.4	**79.6**	**34.1**	93.2-99.6
	Compared to controls	-	**-2 %**	**-18 %**	**-65 %**	-
No of live pups on PND4 before culling	Total	273	233	**157**	**41**	-
	Mean including all litters at PND1#	11.9	11.7	**8.3**	**4.1**	-
	Mean excluding total litter losses	11.9	11.6	**9.2****	**5.9****	-
Died, missing and/or cannibalized pups PND1-PND4	Total	11	20	**55***	**155***	**-**
	% of pup delivered	3.9	7.9	**25.9**	**79.1**	-
Viability index	Mean %#	96.3	92.9	**77.7**	**38.1**	91.9-99.6
	Compared to controls	-	-4 %	**-19 %**	**-60 %**	-
No of live pups	Total	216	186	**148**	**41**	-
	Mean	9.4	9.3	**8.7**	**5.9****	-
Lactation index (mean)		99	96.5	100	100	98.5-100

#: Statistical analysis not performed in the FSR for live birth, viability and lactation indices as well as for mean number of live pups at PND1 and PND4 considering all the females at these time points (including those with total litter loss as reported in the appendix of the FSR).
*/** Differences with control at p ≤ 0.05/0.01
Post-implantation loss = [(Number of implantation sites - Number of delivered pups) / Number of implantation sites] × 100
Live birth index = (Number of live pups on PND1/ Number of delivered pups) × 100
Viability index on PND4 = [Number of surviving pups on day 4 post-partum (before culling)/ Number of delivered pups] × 100
Lactation index = (Number of surviving pups on PND21/ Number of surviving pups on PND4 (after culling)] × 100
HCD submitted during the consultation from 8 OECD TG 443 studies (2017-2022) performed in the same laboratory with the same strain, route of administration not indicated.

On PND 1 and at 500 mg/kg bw/d, there was a statistically significant 20% decrease in mean body weight in both F1 male and female pups when compared with the controls. Female body weight recovered during the lactation period (PND 1 to 21), whereas F1 male pups had a significantly lower mean body weight and mean body weight gain through lactation (-24% and -23%, respectively) compared to the control. High dose male F1 body weight remained lower than controls even after weaning (terminal mean body weight was -8% and -15% compared to controls in C1A and C2A, respectively).

At 225 mg/kg bw/d, F1 male pups had a statistically significant 11% decrease in mean body weight on PND 1, and F1 female pups had a statistically significant decrease in mean PND1 body weight of -9%. Body weight values for both sexes at the mid dose were comparable to controls for the rest of the study.

While C1A contained only 10 males, and C2A contained 5 animals per sex in the high dose group because of insufficient surviving pups at this dose (500 mg/kg bw), there were not enough pups to constitute the high dose groups of the C1B and C2B cohorts. At 225 mg/kg bw and 500 mg/kg bw, F1 animals showed the same narcotic effects as their parents during daily clinical observations. From 225 mg/kg bw, during lactation, F1 pups showed some external findings such as malformed/shortened tails (2/1 pups/litters at the high dose), and hematoma/desquamation/scab (158/8 and 45/9 pups/litters at the mid and high dose, respectively). During lactation, other observations at the high dose included being cold to touch (24/2 pups/litters), dehydration (1/1 pups/litters), hypoactivity (1/1 pups/litters), and thin appearance (1/1 pups/litters).

A functional observational battery (FOB) was performed with 10-week old C2A animals. No effects were recorded on reactivity to manipulation or different stimuli. No abnormal behaviour was observed. Motor activity testing revealed no effects on mean number of horizontal movements and rearings. Based on a lack of hypoactivity or salivation in the FOB and motor activity test, RAC presumed that both were carried out pre-dosing.

In an auditory startle test carried out on PND 24 (±1) for C2A animals, high dose males showed significant decreases in the magnitude of response of up to 45% lower when compared with the control. During the public consultation, industry commented that the effects on auditory startle response (ASR) should be considered a consequence of the

reduced pup body weights at the high dose. The DS responded, citing the North American Free Trade Agreement (NAFTA) Technical Working Group on Pesticides (TWG) Developmental Neurotoxicity Guidance, which states that it is only appropriate to use body weight as a covariate to analyse ASR data when there are no treatment-related effects on body weight (NAFTA, 2016). RAC further noted that, whilst mean body weight was 13% lower in high dose C2A males compared to the controls, the NAFTA guidance also states that some studies have reported no effects on startle response after weight loss of up to 25%. No ASR effects were observed in C2A females.

From 75 mg/kg bw, C2A males showed decreases in three hippocampus measurements following morphometric analysis. Mean entire hippocampus thickness was reduced by 5%, 4% and 12% at 75, 225 and 500 mg/kg bw/d, reaching statistical significance at the high dose. Mean dentate gyrus thickness decreased by 8%, 11% and 19% at the low, mid and high doses (all statistically significant). Lastly, mean cornu ammonis thickness was reduced by 18%, 20% and 15% in the low, mid and high dose groups, respectively. Cerebellum measurements were unaffected. However, RAC noted that, in the four measurements relating to the cerebral cortex, only 1 brain was examined in the control males, and 2 brains in the high dose males; RAC considered this to hamper the assessment. Morphometric analysis did not reveal any effects in C2A females. Additionally, while no high dose animals were included in C2B, no effects on brain weight or morphometric measurements were recorded in C2B at 75 or 225 mg/kg bw.

RAC additionally noted a statistically significant 6% reduction in mean absolute C2A male brain weights at 500 mg/kg bw/d.

Although the EOGRTS study did not include an immunotoxicity cohort, splenic lymphocyte immunophenotyping performed in C1A revealed decreases in the absolute count of splenocytes (-38%, -48% and -40% at low, mid and high dose), B cells (-43%, -55% and -38% at low, mid and high dose), T cells (-41%, -45% and -44% at low, mid and high dose), helper T cells (-44%, -48% and -45% at low, mid and high dose) and cytotoxic T cells (-35%, -38% and -41 at low, mid and high dose) when compared with the controls. RAC noted that the absolute values obtained for the treated groups showed no clear dose-response and were within the HCD range provided during the consultation, while the absolute values for the control group fell outside of the HCD range.

Combined repeated dose toxicity study (Kapp et al., 2003)

In this OECD TG 422 study, combining both reproduction and developmental toxicity screening tests, SD rats (10 per sex per dose group) were administered acetophenone at doses of 0, 75, 225 and 750 mg/kg bw/d (98.80%) via oral gavage from 14 days before mating to lactation day 3. As with the EOGRTS (Anonymous, 2021), there was high perinatal mortality at the top dose.

At the high dose, there was a statistically significant increase in the number of stillborn pups (30 compared to 2 in the control group) and a statistically significant decrease in the number of liveborn pups was observed. This resulted in a low live birth index at the high dose of 78.4%, compared to 98.1, 95.8, 97.3 in the control, low-dose and mid-dose, respectively.

On PND 1-4, there was a statistically significant increase at the top dose in F1 pups dying, missing and/or cannibalised (79 compared to 6 in the control), with 6 females at 750 mg/kg bw experiencing total litter loss. Consequently, the viability index in the high dose group (22.9%) was significantly lower on PND 4 when compared with the control (94.3%). Between PND 1-4, a total of 62 pups died in the high dose group, of which 43 were found to have no presence of milk in the stomach upon necropsy.

At 750 mg/kg bw, there was significant decrease in pup body weight per litter on PND 1 (-20.6%) and 4 (-37.9%). Gross necropsy of stillborn pups showed a single incidence each of cleft palate and oedema, an increase in the incidences of atelectasis (15/4 pups/litters compared to 1/1 in the control) and absence of milk in the stomach (23/5 pups/litters compared to 1/1 in the control) at 750 mg/kg bw. Dermal hypoplasia (12/2 pups/litters compared to in controls), scabbing (8/2 pups/litters compared to 1/1 in controls) and desquamation (3/1 pups/litters compared to 0 in controls) were also observed.

Prenatal developmental toxicity study (Anonymous, 2016a)

In the first PNDT, following OECD TG 414, Wistar rats (35 females in the control and high-dose groups, 25 females in the low and mid dose groups) were orally administered 0, 125, 300 and 750 mg/kg bw of acetophenone (99.79%) daily from GD 5 to 19.

No treatment-related deaths occurred in this study, although one female each in the control and high dose groups were found dead owing to gavage error. Salivation was observed in all top-dose females and a few mid-dose females. There were 33/35, 24/25, 24/24 and 33/35 successful pregnancies in the control, low, mid and high dose, respectively.

In pregnant P0 females, statistically significant decreases in mean body weight compared to controls were observed from GD 8 to 20 at 300 mg/kg bw (up to -8%) and 750 mg/kg bw (up to -12%). Between GD 0 and 20, a reduced mean body weight gain compared to controls of -23% in the mid dose and -37% in the high dose group was recorded, coupled with lower food consumption in the mid dose (-13%) and high dose group (-23%). Additionally, statistically significant reductions in uterus weight compared to controls were recorded in the mid and high dose group (-14% and -25%, respectively). There was also a dose-dependent decrease in mean adjusted maternal body weight compared to controls, which became statistically significant at 300 mg/kg bw (-7%) and at 750 mg/kg bw (-9%). Other clinical signs included transient salivation and reduced spontaneous activity, which were recorded for a few females in the mid dose group and most females in the high dose

group. At 750 mg/kg bw, ataxia and piloerection were recorded in a few females post administration, while apathy and fully closed eyes were recorded in a single female.

Non-statistically significant decreases were recorded for the mean number of implantation sites (-5%, -5% and -7% at the low, mid and high doses, compared to the control) and mean number of foetuses (-6%, -7% and -13%). The DS considered that these decreases were incidental owing to treatment not being initiated before actual implantation. At 750 mg/kg bw there was a slight non-statistically significant increase in the mean number of early resorptions (1.06 compared to 0.41 in the control) and the percentage of post-implantation losses (10.7% compared to 3.74% in the control). RAC noted that these increases were largely driven by 100% implantation loss in one female in the high dose group.

Mean foetus weight in the mid and high dose groups was significantly lower, by -6% and -15%, respectively, compared to the control, resulting in a lower total litter weight at 750 mg/kg bw (-23%). No treatment-related foetal findings were observed following external and visceral examination. Foetuses in the high-dose group showed micrognathia following skeletal examination. At skeletal examination, increases were found at 750 mg/kg bw/d in bilateral pelvic girdle caudal shift (10.92/30.43% foetal/litter incidence compared to 1.13/6.67% in the control) and bilateral full supernumerary 14th thoracolumbar ribs (14.29/43.48% foetal/litter incidence compared to 3.95/23.33% in the control) were (see Table 6 below). RAC noted that caudal shift in the pelvic girdle corresponds to an increase in the number of pre-sacral vertebrae (27 instead of 26 as expected in rats), and noted that therefore the increased incidence of bilateral pelvic girdle caudal shift reflected the increased incidence of bilateral full 14th ribs. While the increases were not statistically significant, they were above the HCD; however, RAC noted that no further information on the HCD was available in the REACH registration dossier to evaluate their reliability.

Table 6: Foetal skeletal findings (taken from page 16 of the RAC opinion; ECHA, 2025)

Dose level (mg/kg bw/d)		**0**	**125**	**300**	**750**	**HCD maximum value**
Pelvic girdle bilateral caudal shift	No of incidences	2	0	4	13	
	Total No of Observed Foetuses	177	121	115	119	
	% Foetal Incidence	1.13	0	3.48	**10.92**	6.2
	No of Litters with at least 1 incidence	2	0	3	**7***	
	Total No of Observed Litters	30	22	21	23	
	% Litter Incidence	6.67	0	14.29	**30.43**	30

Dose level (mg/kg bw/d)		0	125	300	750	HCD maximum value
Rib (14th) bilateral full	No of incidences	7	2	5	17	
	Total No of Observed Foetuses	177	121	115	119	
	% Foetal Incidence	3.95	1.65	4.35	**14.29**	11.5
	No of Litters with at least 1 incidence	7	2	3	10	
	Total No of Observed Litters	30	22	21	23	
	% Litter Incidence	23.33	9.09	14.29	**43.48**	31.58

*Differences with control at p ≤ 0.05. HCD: data provided in the registration dossier. In bold, values above HCD Maximum value.
NB: The reason why only 23 litters among the 32 high-dose litters were investigated for skeletal findings is not available in the registration dossier.

RAC noted that the two abnormalities are categorised as Grey Zone in the DevTox database, with no consensus on whether they should be considered as variations or malformations. They did, however, note that thoracolumbar supernumerary ribs appear to be permanent with unknown implications for offspring health, and have been associated with lower back pain and L4-5 degeneration in humans, according to publications by Makris *et al.*, 2009; DeSesso 2018; and Chernoff, 2010.

Prenatal developmental toxicity study (Anonymous, 2020)

In the second prenatal study, following OECD TG 414, NZW rabbits (22 mated females per dose group) were administered acetophenone at doses of 0, 60, 170 and 500 mg/kg bw/d (99.79%) from GD 6 to 28 by oral gavage.

In the high dose group, 2 females aborted, while a third one was found dead with a red discharge in the cage. Additionally, due to gavage error, 6 females across the control, low and mid dose group were either found dead or sacrificed. All females in the high dose group showed decreased activity and/or abnormal gait 1 hour post-dosing from GD 6 to 27, recovering within the day. Additionally, 2 females in the high-dose group showed laboured and shallow breathing, lying on the side and subdued behaviour on GD 19-20 and GD 9, respectively, but recovered within the day. From the mid dose group upwards, there was a higher frequency of ‘few faeces’. Transient reductions in body weight and body weight gain were observed at 500 mg/kg bw/d, without impact on the terminal body weight compared to controls on GD 29. A decrease in food consumption compared to controls was recorded from GD 6 to 21 at 170 mg/kg bw and from GD 6 to 24 at 500 mg/kg bw. At terminal caesarean, 17, 20, 17 and 18 pregnant females were reported in the control, low, mid, and high dose group, respectively.

A higher mean number of late resorptions was observed at 500 mg/kg bw (0.7) when compared with the control (0.5). Although this was reported not to be statistically

significant, it was above the HCD range provided in the registration dossier (0.1-0.6). This resulted in a slightly higher (not statistically significant) post-implantation loss of 11.13% in the high dose compared to 9.20% in the control group (HCD range: 2.4-11.4%). RAC noted that one high dose female with no viable foetuses (all early resorptions) was excluded from the post-implantation loss calculation. RAC reported that post-implantation loss in the high-dose group to be 16.1% when this high-dose female was included.

A dose-dependent decrease compared to the control was reported for mean foetal weight. This reached statistical significance at the mid and high dose in females (-9% and -13%, respectively) and at the high dose in males/females combined (-9%). No substance-related foetal external, visceral or skeletal abnormalities were reported.

RAC Conclusion

RAC considered the following findings to be relevant for the developmental toxicity classification of acetophenone:

- The OECD TG 443 (Anonymous, 2021) showed a dose-dependent increase in post-implantation loss, reaching statistical significance at 500 mg/kg bw (28.9% versus 16.1% in the control group). The post-implantation loss in OECD TG 414 studies in rats (Anonymous, 2016a) and in rabbits (Anonymous, 2020) was slightly increased at 750 and 500 mg/kg bw, respectively. Thirty stillborn pups were recorded in the high dose group of the OECD TG 422 study (Kapp *et al*., 2003) compared to 2 in the control group. Additionally, the mean number of dead pups on PND 1 (comprising of stillborn pups or pups dead between birth and first check) was statistically significant in the mid and high dose group of the OECD TG 443 study. RAC considered that these data provided clear evidence of adverse effects on offspring viability.
- There was an increase in the total litter loss and a statistically significant increase in the mean number of live pups on PND 1 and PND 4 in the mid and high dose group of the OECD TG 443 study. Post natal mortality was also increased in the OECD TG 422 at 750 mg/kg bw. RAC acknowledged that while narcotic effects may transiently affect maternal care, they noted a lack of correlation between the occurrence of narcotic effects in dams during gestation and lactation as shown by some individual animal data. RAC considered the post-natal offspring mortality not to be a secondary non-specific consequence of other toxic effects.
- The OECD TG 414 study (Anonymous, 2016a) showed structural abnormalities in rats with an increased incidence of the bilateral pelvic girdle shift and the bilateral full supernumerary 14th thoracolumbar rib. RAC considered this effect to have occurred in the presence of moderate maternal toxicity.
- With regards the OECD TG 443 study, RAC considered that the decrease in the audio startle response at the high dose and the hippocampal morphometric effects from the low-dose was treatment-related and adverse.

- A decrease in foetal body weight from PND1 was shown in the OECD TG 443 study (Anonymous, 2021), OECD TG 422 (Kapp *et al*., 2003) study and OECD TG 414 studies (Anonymous, 2016a and Anonymous 2020). RAC considered that the data provided clear evidence of effects on foetal/offspring growth.

Overall, since there were no human data available, RAC concluded that classification with Category 1A was not supported. The animal studies showed clear evidence of death of the organism not secondary to maternal toxicity, clear evidence on offspring/foetal growth, and some evidence of structural abnormality. Therefore, RAC concluded that acetophenone warranted classification as **Repr. 1B; H360D (May damage the unborn child)**.

Lactation

There was no effect of acetophenone on or via lactation reported in the reproduction/developmental toxicity screening test (Kapp *et al*., 2003) or in the extended one-generation study (Anonymous, 2021). RAC noted that no data were available to inform on transfer in the milk or effects on the quality of the milk. Overall, RAC concluded that classification for effects on or via lactation was not warranted.

Classification proposed by the Agency:

During the CLH consultation, the Agency submitted the comment:

'*The DS has proposed a classification of Repr. 1B(F) primarily based on the findings from the OECD TG 443 study (EOGRTS). There are uncertainties with interpretation of the some of the findings from the EOGRTS and therefore we would welcome a discussion regarding the adverse effects on sexual function and fertility based on the following:*

- *Classification as STOT SE 3 has also been proposed, based on the narcotic effects of acetophenone in oral and dermal studies, including the EOGRTS. We support the proposal to classify acetophenone with STOT SE for narcotic effects. Taking into consideration the clear narcotic properties of acetophenone it is possible the apparent adverse effects on sexual function and fertility in particular, dystocia observed in the extended one generation reproduction toxicity study (OECD TG 443) are a secondary consequence of narcosis.*'

RAC agreed with the DS' response stating that three low-dose P0 dams which suffered dystocia were observed to not show signs of narcosis. Additionally, during the gestation period, one female in the mid-dose group showed no sign of narcosis and in the high-dose group hypoactivity was only recorded on GD 2, 3, and 10. While half closed eyes were recorded only on GD 1, 5, and 10. They concluded that the dystocia observed in seven P0 females sacrificed between GD 23-26 were not as a result of narcosis, since clinical signs

associated with narcosis was only recorded in 3 out 7 P0 females, and only on a few isolated days in the gestational period.

The Agency considers that the response provided by the DS is sufficient and therefore agrees with RAC's conclusion on classification. Acetophenone warrants classification as **Repr. 1B; H360FD (May damage fertility. May damage the unborn child)**. Classification is not warranted for effects on or via lactation.

Aspiration hazard

Not assessed in the CLH dossier or RAC opinion.

Environmental hazards

Hazardous to the aquatic environment

Not assessed in the CLH dossier or RAC opinion.

Other hazards

Hazardous to the ozone layer

Not assessed in the CLH dossier or RAC opinion.

Overall conclusion

The Agency has evaluated the RAC Opinion, its rationale and any additional scientific evidence that may have been made available to HSE against the criteria for classification and labelling in the GB CLP Regulation and technical guidance.

The Agency technical report **agrees** with the classification proposed by RAC for the following hazards:

STOT SE 3; H336 (May cause drowsiness or dizziness)

Repr. 1B; H360FD (May damage fertility. May damage the unborn child)

Not classified for acute oral toxicity.

Overall, the conclusion is to **agree** with the RAC opinion.

References

ECHA (2024a) Guidance on the Application of the CLP Criteria, Part 2: Physical Hazards. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 4.0, ref: ECHA-24-G-07-EN. Available at https://www.echa.europa.eu/

ECHA (2024b) Guidance on the Application of the CLP Criteria, Part 3: Health Hazards. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 5.0, ref: ECHA-24-G-06-EN. Available at https://www.echa.europa.eu/

ECHA (2024c) Guidance on the Application of the CLP Criteria, Part 4: Environmental Hazards; and Part 5: Additional Hazards. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, version 4.0, ref: ECHA-24-G-05-EN. Available at https://www.echa.europa.eu/

For all other references, please see the EU CLH report and the EU RAC opinion (available at: https://echa.europa.eu/registry-of-clh-intentions-until-outcome)

CLH (2023) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Acetophenone; Date: 2023; Written by: Ministry of Health, Paseo del Prado, Madrid, Spain; Accessed date: 03/2025.

ECHA (2025) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of Acetophenone; Reference CLH-O-0000007471-76-01/F; Date: 28/11/2024, Accessed date: 03/2025

Documents published as part of the EU CLH process: Source: European Chemicals Agency, http://echa.europa.eu/

Glossary of terms used in Agency technical reports

Agency, the	HSE, acting in its capacity as the GB CLP Agency
AR	Applied radioactivity
ASR	Auditory startle response
ATE	Acute toxicity estimate
BCF	Bioconcentration factor
BOD	Biological Oxygen Demand
bw	Body weight
CAR	Competent Authority Report
CAS	Chemical Abstracts Service
CI	Confidence interval
CL	Confidence limits
CLH	Harmonised Classification and Labelling
CLP	Classification, labelling and packaging (of substances and mixtures)
CO_2	Carbon dioxide
COD	Chemical Oxygen Demand
CV	Coefficient of Variation
d	Day
DAR	Draft Assessment Report
DNT	Developmental neurotoxicity
DOC	Dissolved Organic Carbon
DS	Dossier Submitter
DT	Dissipation time OR degradation time (also DissT or DegT where apparent)
DT_{50}	Dissipation half-life OR degradation half-life (hours or days), see also above
dw	Dry weight
ECHA	European Chemicals Agency
ECx	x% effect concentration
EFSA	European Food Safety Authority
E_rCx	x% effect concentration based on growth rate
EOGRTS	Extended one generation reproductive toxicity study
EU	European Union
FOB	Functional observatory battery
GD	Gestation day
GLP	Good Laboratory Practice
H	Hours
HCD	Historical control data
ID	Identity

K_{OC}	Organic carbon-water partition coefficient
K_{OW}	Octanol-water partition coefficient
LC_x	x% lethal effect concentration
LD	Lactation day
MCL	Mandatory Classification and Labelling
M-factor	Multiplying factor
MW	Molecular weight
NAFTA	National American Free Trade Agreement
NOEC	No-observed effect concentration
NZW	New Zealand White
OECD	Organisation for Economic Co-operation and Development
PND	Postnatal day
PNDT	Prenatal developmental toxicity
QSAR	Quantitative structure-activity relationship
RAC	Risk Assessment Committee
RAR	Renewal Assessment Report
RCOM	Response to comments document
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals regulation
SD	Sprague Dawley
STOT-RE	Specific target organ toxicity – repeated exposure
STOT-SE	Specific target organ toxicity – single exposure
TC C&L	Technical Committee for Classification and Labelling
TG	Test Guideline
TWG	Technical working group
US EPA	United States Environmental Protection Agency
wt	Weight
wwt	Wet weight

Further information

Health and Safety Executive
Chemicals Regulation Division
Redgrave Court
Merton Road
Bootle L20 7HS
GBCLP.GBMCL@hse.gov.uk

This publication is available on the HSE website.

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