Agency technical report on the classification and labelling of:

p-cymene; 1-isopropyl-4-methylbenzene; 3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal; 3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [1]; 4-isopropylbenzaldehyde; cuminic aldehyde [2]; 4-isopropylbenzoic acid; cuminic acid [3]

EC Numbers: 202-796-7; 203-161-7; 231-885-3 [1]; 204-516-9 [2]; 208-642-5 [3]
CAS Numbers: 99-87-6; 103-95-7; 7775-00-0 [1]; 122-03-2 [2]; 536-66-3 [3]

March 2026

Note: This is version 2 of the technical report. The original technical report was published in March 2026. Subsequently, some errors were identified in the summary sections of the report, and a corrected version was published in the April 2026. No changes to the assessment were made, and the overall conclusion of the report (to agree with the classifications proposed in the RAC Opinion for the cyclamal group of substances) remains the same.

Contents

Brief summary

The conclusion of the Agency technical report is that the substances within the cyclamal group should be classified as follows:

Substance name	**Classification**
3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal	Repr. 1B; H360FD (May damage fertility. May damage the unborn child)
p-cymene; 1-isopropyl-4-methylbenzene	Repr. 1B; H360Fd (May damage fertility. Suspected of damaging the unborn child)
3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal 4-isopropylbenzaldehyde; cuminic aldehyde 4-isopropylbenzoic acid; cuminic acid	Repr. 1B; H360Fd (May damage fertility. Suspected of damaging the unborn child)

RAC proposed the inclusion of a new note to accompany these entries in Annex VI of EU CLP:

“The classification of mixtures as reproductive toxicant is necessary if the sum of the concentrations of individual substances covered by this entry, forming the same metabolite, in the mixture as placed on the market is equal to, or above, the applicable generic concentration limit for the assigned category, or a specific concentration limit given in this entry.”

The Agency appreciates the intention of the note and can support it in principle, however the wording of the note will be given further consideration in the Agency Opinion.

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 reproductive toxicity. This was the only hazard class considered in the EU Committee for Risk Assessment (RAC) Opinion. The substance *p*-cymene has an existing entry on the GB MCL list, and is classified as Flam. Liq. 3. (H226); Acute Tox. 3 (H331), Asp. Tox. 1 (H304) and Aquatic Chronic 2 (H411). These hazard classes have not been reassessed and these classifications should remain in the GB MCL list entry for this substance.

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:

- *p*-cymene; 1-isopropyl-4-methylbenzene;
- 3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl 3-(4-isopropylphenyl)propanal;
- 3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal;
- 4-isopropylbenzaldehyde; cuminic aldehyde;
- 4-isopropylbenzoic acid; cuminic acid.

according to the GB CLP criteria.

Table 1. Information considered in the scientific assessment

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

[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 2a. Current and proposed classification and labelling (*p*-cymene)

	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	601-094-00-1	*p*-cymene; 1-isopropyl-4-methylbenzene	202-796-7	99-87-6	Flam. Liq. 3 Acute Tox. 3 Asp. Tox. 1 Aquatic Chronic 2	H226 H331 H304 H411	GHS02 GHS06 GHS08 GHS09 Dgr	H226 H331 H304 H411		Inhalation: ATE = 3 mg/L (vapours)	
EU dossier submitter's proposal	601-094-00-1	*p*-cymene; 1-isopropyl-4-methylbenzene	202-796-7	99-87-6	**Add** Repr. 1B	**Add** H360FD		**Add** H360FD			**Add** Note *
EU RAC opinion	601-094-00-1	*p*-cymene; 1-isopropyl-4-methylbenzene	202-796-7	99-87-6	**Add** Repr. 1B	**Add** H360Fd		**Add** H360Fd			**Add** Note *
Agency technical report conclusion	601-094-00-1	*p*-cymene; 1-isopropyl-4-methylbenzene	202-796-7	99-87-6	**Add** Repr. 1B	**Add** H360Fd		**Add** H360Fd			**Add** Note *
Resulting MCL entry on GB MCL list	601-094-00-1	*p*-cymene; 1-isopropyl-4-methylbenzene	202-796-7	99-87-6	Flam. Liq. 3 Acute Tox. 3 Repr. 1B Asp. Tox. 1 Aquatic Chronic 2	H226 H331 H360Fd H304 H411	GHS02 GHS08 GHS06 GHS09 Dgr	H226 H331 H360Fd H304 H411		Inhalation: ATE = 3 mg/L (vapours)	Note *

* New note: The classification of mixtures as reproductive toxicant is necessary if the sum of the concentrations of individual substances covered by this entry, forming the same metabolite, in the mixture as placed on the market is equal to, or above, the applicable generic concentration limit for the assigned category, or a specific concentration limit given in this entry.

Table 2b. Current and proposed classification and labelling (cyclamal)

	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		No current entry.									
EU dossier submitter's proposal	TBD	3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal [1]; 3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [2]; 4-isopropylbenzaldehyde; cuminic aldehyde [3]; 4-isopropylbenzoic acid; cuminic acid [4]	203-161-7 [1]; 231-885-3 [2]; 204-516-9 [3]; 208-642-5 [4]	103-95-7 [1]; 7775-00-0 [2]; 122-03-2 [3]; 536-66-3 [4]	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note*
EU RAC opinion	TBD	3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl) propanal	203-161-7	103-95-7	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note *
Agency technical report conclusion	TBD	3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl) propanal	203-161-7	103-95-7	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note *
Resulting MCL entry on GB MCL list	TBD	3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl) propanal	203-161-7	103-95-7	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note *

TBD: to be determined

* New note: The classification of mixtures as reproductive toxicant is necessary if the sum of the concentrations of individual substances covered by this entry, forming the same metabolite, in the mixture as placed on the market is equal to, or above, the applicable generic concentration limit for the assigned category, or a specific concentration limit given in this entry.

Table 2c. Current and proposed classification and labelling (substances other than *p*-cymene and cyclamal)

	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		No current entry.									
EU dossier submitter's proposal	TBD	3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal [1]; 3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [2]; 4-isopropylbenzaldehyde; cuminic aldehyde [3]; 4-isopropylbenzoic acid; cuminic acid [4]	203-161-7 [1]; 231-885-3 [2]; 204-516-9 [3]; 208-642-5 [4]	103-95-7 [1]; 7775-00-0 [2]; 122-03-2 [3]; 536-66-3 [4]	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note*
EU RAC opinion	TBD	3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [1] 4-isopropylbenzaldehyde; cuminic aldehyde [2] 4-isopropylbenzoic acid; cuminic acid [3]	231-885-3 [1] 204-516-9 [2] 208-642-5 [3]	7775-00-0 [1] 122-03-2 [2] 536-66-3 [3]	Repr. 1B	H360Fd	GHS08 Dgr	H360Fd			Note *
Agency technical report conclusion	TBD	3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [1] 4-isopropylbenzaldehyde; cuminic aldehyde [2]	231-885-3 [1] 204-516-9 [2]	7775-00-0 [1] 122-03-2 [2]	Repr. 1B	H360Fd	GHS08 Dgr	H360Fd			Note *

	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)		
		4-isopropylbenzoic acid; cuminic acid [3]	208-642-5 [3]	536-66-3 [3]							
Resulting MCL entry on GB MCL list	TBD	3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [1] 4-isopropylbenzaldehyde; cuminic aldehyde [2] 4-isopropylbenzoic acid; cuminic acid [3]	231-885-3 [1] 204-516-9 [2] 208-642-5 [3]	7775-00-0 [1] 122-03-2 [2] 536-66-3 [3]	Repr. 1B	H360Fd	GHS08 Dgr	H360Fd			Note *

TBD: to be determined

* New note: The classification of mixtures as reproductive toxicant is necessary if the sum of the concentrations of individual substances covered by this entry, forming the same metabolite, in the mixture as placed on the market is equal to, or above, the applicable generic concentration limit for the assigned category, or a specific concentration limit given in this entry.

Background

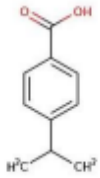
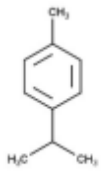
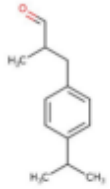
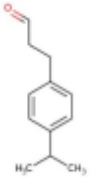
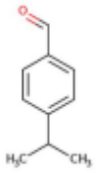
Active substance in Plant Protection Products: ☐

Active substance in Biocidal Products: ☐

Chemical registered under REACH: ☒

The EU CLH proposal covers five structurally similar substances referred to as the cyclamal group in the RAC Opinion and this technical report.

Figure 1. Structures of the members of the cyclamal group considered in this technical report. Taken from ECHA (2025)

4-isopropyl benzoic acid (4-iPBA)	*p*-cymene	3-*p*-cumenyl-2-methylpropion aldehyde (= cyclamal)	3-(*p*-cumenyl) propion aldehyde (= cyclemax)	4-isopropyl benzaldehyde (= cuminic aldehyde)
208-642-5	202-796-7	203-161-7	231-885-3	204-516-9
536-66-3	99-87-6	103-95-7	7775-00-0	122-03-2
				

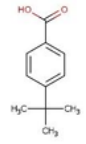
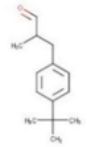
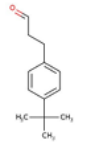
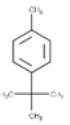
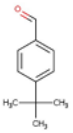
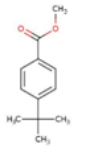
For one of these substances – 4-iPBA – the EU dossier submitter (DS; Swedish Chemicals Agency) was unable to find any information on uses. The other four substances are used as fragrances/perfumes in a range of products (e.g., cosmetics, personal care products, cleaning products, washing agents, polishes/wax blends, rinsing agents for textiles) (CLH, 2023). The substance *p*-cymene is also one of the ingredients of the active substance terpenoid blend QRD460. Both *p*-cymene and 4-isopropylbenzaldehyde are registered as intermediates under REACH. At the time the CLH report was drafted, the Swedish Products Register listed products containing 3-*p*-cumenyl-2-methylpropionaldehyde, *p*-cymene and 4-isopropylbenzaldehyde at concentrations ranging from 0.00001 to 10% (median range from 0.005% to 0.093%).

Grouping / read-across justification

The DS has grouped these substances together on the basis of structural similarity (benzene ring with a substituent that can degrade to a carboxylic acid group and an isopropyl group in the para position) and experimentally demonstrated or modelled formation of the metabolite 4-iPBA (*in vitro* and *in vivo* toxicokinetic studies and OECD QSAR Toolbox). Based on these properties, the DS defined a category in accordance with the REACH guidance on grouping of chemicals which complies with the OECD principles for the validation of chemical grouping.

The DS prepared a separate CLH dossier covering a group of structurally closely related substances referred to as the “bourgeonal group” (see Figure 2). The group includes TBBA, which is also a common metabolite of the other group members. TBBA differs from 4-iPBA only by a methyl group at the benzylic carbon.

Figure 2. Members of the bourgeonal group. Taken from ECHA (2025)

4-*tert*-butylbenzoic acid (TBBA)	2-(4-*tert*-butylbenzyl) propion aldehyde (= lysmeral)	3-(4-*tert*-butylphenyl) propion aldehyde (= bourgeonal)	4-*tert*-butyltoluene	4-*tert*-butylbenz aldehyde	methyl 4-*tert*-butyl benzoate
202-696-3	201-289-8	242-016-2	202-675-9	213-367-9	247-768-5
98-73-7	80-54-6	18127-01-0	98-51-1	939-97-9	26537-19-9
					

The DS recognised that substances of both groups are metabolised in a similar way and have similar properties in terms of reproductive toxicity; however, as the strength of evidence for developmental toxicity differs between the substances, the DS decided to separate the two groups and to make separate proposals for developmental toxicity.

For the cyclamal group, the grouping approach is supported by similar physicochemical properties, toxicokinetic and toxicological datasets. Toxicity data relevant for the assessment of reproductive toxicity are available for all group members, except for 4-isopropylbenzaldehyde, and indicate a similar reproductive toxicity profile.

The DS summarised *in vivo* toxicokinetic studies for p-cymene (single oral and inhalation exposure) and cyclamal (28-d, oral) which demonstrated the formation of 4-iPBA in rats after oral exposure. Following inhalation exposure to p-cymene, the formation of 4-iPBA was reported in rats and guinea pigs. Following repeated (28-day) oral exposure in rats to cyclamal, 4-iPBA-CoA (Coenzyme A) conjugate was detected in the testis in a dose-dependent manner, although levels were 100s of times lower than in the liver. The same

study detected high circulating levels of free 4-iPBA in the plasma (Study report, 2019; also reported by Natsch *et al.,* 2021 and Laue *et al.,* 2020; see CLH (2023) for further information).

Comparative *in vitro studies* have been carried out with cyclamal and cyclemax using rat, rabbit, mouse and human primary hepatocytes.

In the first comparative *in vitro* test (Laue *et al.,* 2020), plated rat, rabbit and human hepatocytes were exposed to cyclamal (5 and 50 µM) for 0.5, 4, 8 (rabbit only) and 22h (in triplicate). The highest level of 4-iPBA-CoA was detected in rat hepatocytes and the level was stable over time (22h). In rabbit hepatocytes, 4-iPBA-CoA levels were about 20-fold lower than in rats, and levels decreased over time. In human hepatocytes, levels were lower than in rat or rabbit cells for the higher concentration, but equal to the rabbit levels for the lower concentration. As in the rabbit, 4-iPBA-CoA levels in human hepatocytes decreased over time. Comparable results were obtained for lysmeral and the respective metabolite TBBA-CoA, member of the bourgeonal group.

In the second comparative *in vitro* test (Natsch *et al*., 2021), cryopreserved primary hepatocytes from mice, rats, rabbits and humans were incubated with 10 and 100 µM cyclamal for 0, 1 and 4 hours (in duplicates). Five main metabolite peaks were observed: the direct oxidation product (cyclamen acid) and several glucuronide conjugates, i.e. the glucuronide of cyclamen alcohol, the glucuronide of a desaturated cyclamen alcohol as well as the glucuronide of a hydroxylated cyclamen alcohol. These metabolites occurred at high levels in all four species. In rats, cyclamen acid was also further degraded to 4-iPBA. Levels of 4-iPBA were below the detection limit in rabbit, human and mouse hepatocyte incubations.

In the third comparative *in vitro* test, mouse, rat, rabbit and human hepatocytes were exposed to cyclemax at 1, 10 and 100 µM for 0, 1 or 4h (Study report, 2012). Eight metabolites were detected; 4-iPBA was observed at low levels in mouse, rat and rabbit hepatocytes (<5% at 100 µM after 1 and 4h in mouse) but was not detected in human hepatocytes.

The formation of benzoic acid derivatives and CoA conjugates in primary hepatocytes was investigated for cyclamal and cyclemax (Laue *et al.,* 2017). Rat hepatocytes in suspension were incubated in the presence of 100 µM of the test chemicals for 4 h. Benzoic acid derivatives were determined by GC-MS at 0.5, 4 and 22 h. Formation of CoA conjugates in plated rat hepatocytes following 0.5, 4 and 22 hours of exposure to the chemicals at 5 and 50 µM was assessed by LC-HRMS. For both cyclamal and cyclemax, benzoic acid derivatives, including 4-iPBA, could be determined in hepatocytes in suspension and for both substances, as well as for 4-iPBA, high and stable benzoic acid-CoA conjugates were detected in plated hepatocytes.

For 4-isopropylbenzaldehyde (cuminic aldehyde) no toxicokinetic study was available. However, a profiling scheme built in the OECD (Q)SAR Toolbox predicts that 4-iPBA will be formed from this substance. The profiling scheme also demonstrated the formation of 4-iPBA for cyclemax, but not for p-cymene or cyclamal. However, formation of 4-iPBA was demonstrated *in vivo* for p-cymene and cyclamal.

On the basis of the above, RAC concluded that for all four of these structurally related substances, the formation of 4-iPBA had been demonstrated either *in vivo*, *in vitro* or by QSARs.

The comparative *in vitro* tests reported the highest levels of 4-iPBA and 4 iPBA-CoA in rat hepatocytes, compared to mice, rabbit or human hepatocytes. The data also suggest that the conjugates are more stable in the rat. However, RAC noted that in all tested species the formation of 4-iPBA and 4 iPBA-CoA could be demonstrated *in vitro* and/or *in vivo*, including in humans.

The available *in vivo* studies show that members of the cyclamal group are readily taken up following oral and inhalation exposure, and are distributed in the body. For cyclamal, distribution to the liver and testis was demonstrated. RAC considered that the testicular toxicity seen with p-cymene, cyclemax and 4-iPBA was evidence that these substances (and/or their metabolites) were also distributed to the testis.

Excretion has not been extensively studied for the members of the cyclamal group, but for p-cymene 60-80% of the substance was eliminated in the urine following both oral and inhalation exposure (Walde *et al.,* 2009).

Overall, RAC supported the grouping and read-across approach proposed by the DS. The Agency has considered the available information and also supports the grouping and read-across approach for these substances.

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

Physical Hazards

Not assessed in the CLH report or RAC Opinion.

Health Hazards

Acute Toxicity

Not assessed in the CLH report or RAC Opinion.

Specific target organ toxicity – single exposure (STOT SE)

Not assessed in the CLH report or RAC Opinion.

Skin corrosion/irritation

Not assessed in the CLH report or RAC Opinion.

Serious eye damage/irritation

Not assessed in the CLH report or RAC Opinion.

Respiratory sensitisation

Not assessed in the CLH report or RAC Opinion.

Skin sensitisation

Not assessed in the CLH report or RAC Opinion.

Specific target organ toxicity – repeated exposure (STOT RE)

Not assessed in the CLH report or RAC Opinion.

Germ cell mutagenicity

Not assessed in the CLH report or RAC Opinion.

Carcinogenicity

Not assessed in the CLH report or RAC Opinion.

Reproductive toxicity

Classification agreed by RAC:

Adverse effects on sexual function and fertility

There were no human data available for any of the substances in the cyclamal group. The animal studies relevant for the assessment of adverse effects on sexual function and fertility were as follows:

Studies with p-cymene:

- a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422, GLP) in rats, oral route

- a 14-day study (OECD TG 407, non-GLP) in rats, oral gavage

Studies with 3-p-cumenyl-2-methylpropionaldehyde (cyclamal):

- a one-generation reproduction toxicity study (OECD TG 415, GLP) in rats, oral gavage

- a 28-day study (non-guideline, non-GLP) in rats, oral gavage

- a 90-day repeated dose toxicity study (OECD TG 408, GLP) in rats, oral gavage

- a 14-day study (non-guideline, non-GLP), in rabbits, oral gavage

Studies with 3-(p-cumenyl)propionaldehyde (cyclemax):

- 14-day study (non-guideline, non-GLP) in rats, oral gavage

- 14-day study (non-guideline, non-GLP), rabbits, oral gavage

Studies with 4-isopropylbenzoic acid (4-iPBA):

- 5-day study (non-guideline, GLP not indicated), in rats, oral gavage

Studies with 4-isopropylbenzaldehyde:

- No data on reproductive or chronic toxicity available.

p-cymene

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422, GLP; Study report, 2019), Sprague-Dawley rats (10/sex/group) were administered doses of 0, 50, 100, 200 mg/kg bw/d p-cymene via oral gavage. The duration of treatment was as follows: males – 2 weeks prior to cohabitation, during cohabitation (up to 2 weeks), continuing until termination (approximately 35 days); females - 2 weeks prior to cohabitation, cohabitation (up to 2 weeks) and during gestation and lactation continuing until LD 13 (approximately 63 days).

In the P generation there were no treatment-related effects on food consumption, body weight or body weight gain. No clinical signs were reported except in one female at the top dose; this female was in poor condition and euthanised on presumed GD 24 due to animal welfare reasons. The remaining females at the top dose were euthanised early due to non-pregnancy.

Liver weights were statistically significantly increased in males at the top dose (abs: + 27%, rel: + 41%) and in females at the mid dose (abs: + 26%, rel: + 22%; no data available for females at the top dose owing to early euthanasia). Hepatocellular hypertrophy (diffuse or centrilobular) was reported from the low dose. In the kidneys, effects were seen in males at the top dose: a marginal increase in the incidence and severity of hyaline droplet accumulation, and 2/5 had minimal tubular epithelial vacuolation. Clinical biochemistry findings included decreases in triglycerides (≥ 100 mg/kg bw/d: -50 to 52% in males only), increases in alkaline phosphatase activity (+79% in females at 100 mg/kg bw/d and + 45% in males at 200 mg/kg bw/d) and decreases in albumin (-9% in females at 100 mg/kg bw/d). Increases in blood urea nitrogen (+50%) were seen in top dose males. Minor changes in haematology were reported in top dose males (increase in reticulocytes + 30% and related increases in red blood cell distribution + 7%), and considerably lower T4 values were recorded in males from the mid dose. However, T4 levels did not follow a dose-response and TSH levels were mostly below the limit of detection. There were no effects on thyroid weight or histopathology findings in the thyroid. Reduction of hindlimb grip strength was observed in males of the top dose.

At the top dose, males of the P generation were affected by bilateral testicular germ cell degeneration, depletion and/or sperm retention. These testicular findings were associated with varying degrees of luminal cell debris and reduced sperm with or without cribriform change which were present bilaterally in the epididymis. The absolute weights of male reproductive organs were also reduced at the top dose (testes: -14%, epididymides: -14%, both statistically significant; levator ani-bulbocavernosus muscle: -15%, not statistically significant). Two top dose males had unilateral or bilateral small testes; one of these males also had a small prostate (without histopathology findings) and another male of this group had a small levator ani-bulbocavernosus muscle (tissue not examined microscopically). At the mid-dose, marginal bilateral sperm retention in testis was seen in some males, two of them also had decreased sperm in the epididymis (with or without cribriform change). Unilateral or bilateral seminiferous tubular atrophy, with or without luminal cell debris and reduced sperm in the epididymis, was observed in one male of the mid- and one male of the low dose group.

In females, there were alterations in oestrus cyclicity at the top dose, with fewer animals with regular cycles during the pre-cohabitation period. Reductions in fertility were seen from 100 mg/kg bw/d, as the number of pregnant females was statistically significantly reduced (number of pregnant females: 9, 9, 4 and 0 at 0, 50, 100 and 200 mg/kg bw/d, respectively). Eighteen females across all groups, including controls, were euthanised early. Seventeen of these females (1/10 in control, 1/10 at 50 mg/kg bw/d, 6/10 at 100 mg/kg bw/d and 9/10 at 200 mg/kg bw/d) were euthanised on GD 25 due to failure to become pregnant. There was a dose-related increase in pre-implantation loss (1.8%, 5.9% and 7.1% in controls, low and mid dose).

As there were no pregnant females at the top dose, the F1 generation could only be investigated for the low and mid-dose. At the mid dose, the number of litters was statistically significantly lower compared to the control group (number of litters at 0, 50 and 100 mg/kg bw/d was 9, 9 and 4, respectively). Live birth index and post-implantation survival index were also reduced at the mid dose (-5.7% and -7.7%, respectively, both statistically significant). Only one of the four litters at the mid dose had 100% viability (vs 9/9 in the controls). Mean litter body weight was statistically significantly lower at the mid dose on PND 1, but body weights were comparable with controls on PND 4, 7, 11 and 13. No other relevant findings were reported in the F1 generation.

Overall, there was clear evidence of testicular toxicity and spermatotoxicity at the top dose in the absence of severe general toxicity. Similar effects were seen in a few animals at the mid dose, and one animal in the low dose group had testicular atrophy. Lower testis and epididymis weights were associated with germ cell degeneration/depletion and decreased sperm, respectively. In females, abnormal cyclicity was reported at the top dose. Fertility index was severely affected from the mid-dose, with no pregnancies at the top dose. Live birth index and post-implantation survival were statistically significantly reduced in the mid

dose group. Mean pup weight on PND 1 was statistically significantly lower at the mid-dose compared to controls (no pups were produced at the top dose).

In a short-term repeated dose toxicity study (OECD TG 407, non-GLP; Study Report, 2018), p-cymene was administered to Sprague Dawley rats (3/sex/group) via oral gavage at doses of 0, 50, 150 and 500 mg/kg bw/d for 14 consecutive days. No information regarding statistical analysis was provided.

No clinical signs were reported, although one female at the top dose was euthanised on day 13 due to animal welfare reasons. In females, food consumption was reduced at the top dose and terminal body weights were reduced compared to controls from the mid-dose (-9% and -14% at the mid and top dose, respectively). In males, terminal body weights were reduced at the top dose (-12%). Liver weights were increased in both sexes from the mid dose (+29%, 50% in males, +29%, +23% in females at 150 and 500 mg/kg bw/d, respectively), and spleen weights were reduced at the top dose (>20% in both sexes). Small/soft testes were reported at the top dose (2/3 males), and small testes and epididymides were reported at the mid dose (1/3 males). In females, small uterus and cervix were reported at the top dose (1/3). RAC considered that no firm conclusions could be drawn from this study owing to the small number of animals used but noted that the results were in line with those of other studies on substances in the cyclamal group.

3-p-cumenyl-2-methylpropionaldehyde (cyclamal)

In a one-generation reproduction toxicity study (OECD TG 415, GLP; Study Report, 2011a), Sprague Dawley rats (25/sex/group) were given doses of 0, 25, 75 and 150 mg/kg bw/d of cyclamal via oral gavage. Males of the P generation were exposed for 83 days prior to cohabitation, during cohabitation up until the day before sacrifice. Females of the P generation were exposed two weeks prior to cohabitation, up until GD 25 (non-pregnant females) or up until PND 22 (for females that delivered pups). F1 animals were not directly dosed but were exposed *in utero* and via milk. Mating was with a “cross-over” design, in which treated males were mated with un-treated females and vice versa. F1 animals were weaned on PND 22, and then 25 pups/sex were selected for continuous observations (until PND 58-60). The remaining animals was necropsied. All results described below were statistically significantly different from the control values.

The only clinical sign reported was a slight/moderate increase in salivation in top-dose males. Food consumption was unaffected in males, but statistically significant reductions in body weight gain were reported, leading to dose-related decreases in mean body weights in treated males by day 134 (0%, -3% and -7% at 25, 75 and 150 mg/kg bw/d). Food consumption was reduced in females (apart from during gestation). Body weight gain was also reduced, leading to slight decreases in mean body weight (<10%) compared to controls.

In treated males there was a decrease in absolute adrenal weights (-11%, -14% at the mid- and top dose) and absolute brain weight (-3%, -5% at the mid- and top dose) and increases in kidney weight at the top dose (+13%). Relative liver weights were increased in treated males (+10%, +19% at the mid and top dose) and females (+7%, +17%, +19% at the low, mid and top dose). Relative testis weight (left and right) was reduced by 11% at the top dose while absolute and relative weight of the epididymides was increased in the top dose group; this was explained by the presence of masses in the cauda epididymis.

When treated males were mated with untreated females, only one pregnancy was achieved (1/24) at the top dose and the dam did not deliver a litter (the fertility index was 92%, 100%, 87.5% and 4.3% at 0, 25, 75 and 150 mg/kg bw/d, respectively). No motile sperm were present in top dose animals or in 13/25 males at the mid dose. Sperm count and sperm density (Cauda epididymis) were also reduced at the mid dose (-30% and -36%, respectively). At the top dose, an increase in white fibrous masses in the epididymis was reported in 10 males (vs 0 in control). Microscopy revealed the presence of moderate to marked sperm granulomas, with mild to moderate epithelial degeneration, in these masses. In females there was a decrease in absolute and relative non-gravid uterus weight at the mid (-18% and -19%, respectively) and top dose (-20% and -22%, respectively) and left and right ovary weight was reduced by 17% at the top dose.

When untreated males were mated with treated females, pregnancy occurred in 25 (100%), 24 (96%), 24 (96%) and 24 (96%) dams in the control, low-, mid- and top dose groups, respectively. At the top dose, there was a decrease in implantation sites (-11%), an increase in the number of dams with all pups dying between PND 1 to 5 (+16.7% vs 0% in control), an increase in the number of stillborn pups/litter (2.7% vs 0% in control) and decreases in the number of pups delivered per litter (-15%) and number of liveborn pups/litter (-17%). Pup mortality was increased in the low and top dose groups, and pup viability index was reduced at the top dose (75.7% vs 96.3% in controls). Further observations in the F1 generation are discussed in the section on developmental toxicity.

In summary, severe spermatotoxicity was observed at 150 mg/kg bw/d, which correlated with complete infertility at this dose (fertility index of 0%), when treated males were mated with untreated females. Sperm count and density was statistically significantly reduced compared to controls at the mid dose, and fertility index at that dose was reduced to 4.3%. Fertility index was also reduced in the low dose group (87.5%). When treated females were mated with untreated males, the majority of females became pregnant (96% in all dose groups, compared to 100% in controls), but reduced number of implantation sites per delivered litter, reduced number of live born pups per litter and increased number of stillborn pups were observed at the top dose. There was no marked toxicity among treated paternal animals. Among treated maternal animals, body weights were slightly reduced throughout the study (<10%). The non-gravid uterus weight was statistically significantly reduced from the mid dose (up to -20%) and ovary weight was reduced at the top dose.

In a 28-day study (non-guideline, non-GLP; Study Report, 2020a), Wistar rats (5 males/ group) were administered cyclamal at 0, 30, 100 or 300 mg/kg bw/d via oral gavage. No mortality or clinical signs were reported. Final body weight was reduced at the top dose (-11%).

Gross lesions were observed in the epididymis at the top dose, including a focal nodule in the tail of the epididymis (3/5 males). Sperm effects were reported from the mid dose: decreased sperm motility (-24%, -78%* at the mid and top dose), decreased progressive sperm (-30%, -90%* at the mid and top dose), decreased cells with normal morphology (-13%, -96% and the mid and top dose), decreased cells with coiled tail (-61%, -87% at the mid and top dose), increased incidence of cells with detached head (+343%, +146% at the mid and top dose)) increased incidence of cells with abnormal neck (+600%, +800%). At the top dose, there was reduced total sperm count in epididymis (- 39%), increased degeneration of elongating spermatids (all animals) and increased degeneration of round spermatids (1/5males). No effects were seen in the low dose group. Where indicated with * the effects were statistically significant.

In a 90-day repeated dose toxicity study (OECD TG 408, GLP; Study Report, 2020b), Wistar rats (10/sex/dose) were dosed with 0, 15, 30 and 120 mg/kg bw/d cyclamal by oral gavage. Clinical signs were limited to salivation after dosing (some animals at the mid and top dose), some incidences of fur loss, scabs and incidental erected fur. At the top dose, terminal body weights were reduced (-9% in males, -7% in females). Clinical biochemistry changes included a decrease in protein concentration at the top dose (-14% in males, -17% in females). Top dose males also had reduced total cholesterol and HDL cholesterol (-28% and -31%, respectively). Absolute and relative liver weights were increased in females of all dose groups (relative liver weight were +22%, +27% and +44% at 15, 30 and 120 mg/kg bw/d, respectively), while in males an increase in relative liver weight was seen at the top dose (+21%). Absolute and relative kidney weights were increased in females at the mid (+8% and +11%, respectively) and top dose (+8% and +16%, respectively). In males, relative kidney weight was increased in the top dose group (+8%). In females, relative heart weight was increased in the mid and top dose group (+13% and +12%, respectively). There were no histopathological findings in any of these tissues, apart from the liver, where hepatocellular hypertrophy was observed in males ≥ 30 mg/kg bw/d and in females ≥ 15 mg/kg bw/d, generally of mild severity. Male reproductive organ weights were affected by treatment, including a decrease in seminal vesicle gland weight from the mid-dose (relative weight: -19%) and top dose (relative weight: -28%, absolute weight: -20%), a decrease in absolute epididymis weight at the top dose (-13%) and an increase in relative testis weight at the top dose (+14%), which was considered to be secondary to the lower terminal body weight in this group. A unilateral nodule was noted in the epididymis of a top dose male, which was associated with microscopically identified

sperm granuloma. Two further males at this dose had sperm granuloma in epididymis (3/10, mild degree).

No effects on sperm were noted at the low or mid dose. At the top dose (120 mg/kg bw/d), a decrease in the percentage of motile sperm (32% vs 71% in controls), percentage of progressive sperm (6% vs. 25% in controls), number of cells with normal morphology (48 vs. 181 in controls) and number of cells with a coiled tail (2 vs. 13 in controls) were reported, along with an increase in the number of cells with detached head and abnormal neck (103 vs 3 in controls). All results described for this study were statistically significantly different from the control values.

Overall, there were clear effects on male reproductive organs and spermatotoxicity in this study. There was no marked general toxicity up to the top dose of 120 mg/kg bw/d.

In a 14-day study (non-guideline, non-GLP; Study Report, 2011b), New Zealand White rabbits (5 males/group) were administered 0, 30, 100 and 300 mg/kg bw/d of cyclamal by oral gavage for 14 days. No indication was given as to whether effects in this study were statistically significant.

No deaths, adverse clinical signs or effects on body weight were reported. At the top dose, there was an increase in absolute and relative liver weights (+18% and +21%, respectively) and in absolute and relative kidney weights (+11% and +13%, respectively). In the sperm parameters, there was a treatment-related decrease in the mean number of motile sperm (-5%, - 13% and -31% at 30, 100 and 300 mg/kg bw/d, respectively) and a treatment-related decrease in total sperm counts (-9%, -12%, -31% at 30, 100 and 300 mg/kg bw/d, respectively).

In summary, dose-related effects on the mean number of motile sperm and total sperm count were observed in rabbits in the absence of severe general toxicity.

3-(p-cumenyl)propionaldehyde (cyclemax)

In a 14-day study (non-guideline, non-GLP), Sprague Dawley rats (10 males/group) were administered doses of 0, 25, 75 and 250 mg/kg bw/d by oral gavage for 14 consecutive days. No deaths or clinical signs were reported. At the top dose, body weights were reduced (no details on magnitude available). In mid- and top dose groups, liver weights were increased but without histopathological findings. The weight of seminal vesicles and prostate was decreased at the top dose, and microscopic changes were seen in the testes, epididymides and seminal vesicles (including atrophy). At the top dose, it was not possible to determine the number and percentage of motile sperm, number of non-motile sperm or total sperm count from the vas deferens. Sperm count and sperm density from the cauda epididymis were reduced at the mid (statistically significant) and top dose (not statistically significant). An increase in abnormal sperm, sperm with detached heads or no heads was reported from the mid dose.

In summary, reduced organ weights and microscopic changes in male reproductive organs of top dose animals and sperm parameters were affected from the mid dose.

In a 14-day study (non-guideline, non-GLP; Study Report B), New Zealand White rabbits (5 males/group) were administered cyclemax at doses of 0, 10, 30 and 100 mg/kg bw/d via oral gavage. Since no toxicity was observed, a further dose of 300 mg/kg bw/d was assessed in an extension to the study.

No mortality, clinical signs or effects on food consumption, body weight or body weight gain were reported. Relative liver and kidney weights were slightly increased at the top dose, but the finding was not statistically significant. There was an increase in microscopic findings in the testes and epididymis in all animals at the top dose – these animals had minimal to mild increases in residual bodies in testes, 3/5 animals had mild or minimal depletion of spermatozoa in the epididymides, and two of these rabbits had detachment of the seminiferous tubules of the testes.

At 300 mg/kg bw/d, there was an increase in abnormal sperm (38%) when compared to the controls (and also when compared to the values from the initial study, where the top dose was 100 mg/kg bw/d: the observed range of abnormal sperm: 15.4% to 29.2%). Abnormal sperm consisted mainly of sperm with detached heads. According to the study report, this increase could be attributed to two rabbits which had 49.5% and 60% abnormal sperm. RAC noted that the animals in the 300 mg/kg bw/d group had the highest percentage of abnormal sperm pre-dosing, i.e. 23.7%, as compared to the concurrent control with 17.8% abnormal sperm and as compared to the other groups where the values ranged from 12.9% to 17.7%.

In summary, microscopic findings were seen in the testes and epididymis of rabbits at 300 mg/kg bw/d in the absence of adverse general toxicity. The percentage of abnormal sperm was highest at 300 mg/kg bw/d and the abnormal sperm consisted mainly of sperm with detached heads.

4-isopropylbenzoic acid (4-iPBA):

In a 5-day study (non-guideline, non-GLP; Natsch *et al.,* 2021), CD rats (6 males/group) were administered doses of 0, 15, 50 and 150 mg/kg bw/d, by oral gavage. No clinical signs were reported. Food consumption was reduced at the top dose. Absolute and relative weights of the epididymides were increased (+20%) at the top dose, with the cauda epididymis weight increasing by 43% (statistically significant). Histopathology revealed the following changes at the top dose: minimal to slight interstitial inflammatory cells in the epididymides (in 5/6 animals), apoptotic epithelial cells (4/6), degenerate spermatogenic cells in the ducts (5/6), epithelial hyaline droplets (4/6) and reduced numbers of spermatozoa (4/6) in epididymides. A dose-related increase in the incidence of seminiferous tubule vacuolation was seen in the testes (1/6, 2/6 and 4/6 at the low, mid and high dose respectively) and in the top dose testes degenerate spermatocytes (4/6)

and spermatid giant cells (3/6) were observed. Sperm analysis did not reveal treatment-related effects on sperm motility, concentration or morphology.

In summary, five days of treatment with 4-iPBA resulted in adverse effects on the testis (seminiferous tubular vacuolation at all doses) and epididymides at minimal general toxicity or absent general toxicity.

4-isopropylbenzaldehyde

- No data on reproductive or chronic toxicity available.

Discussion

The following text is copied directly from the RAC Opinion:

The available data for the members of the cyclamal group demonstrate adverse effects on male reproductive organs and spermatogenesis, which, where assessed, resulted in adverse effects on fertility, with complete infertility at higher doses. Some effects were also seen on female reproductive organs, oestrus cyclicity and female fertility. These effects were seen in the absence of general toxicity or in the absence of marked general toxicity, indicating that they were not secondary unspecific consequence of general toxicity.

The majority of studies were carried out in rats which consistently demonstrated adverse effects on male sexual function and fertility for all tested members of the cyclamal group. The effects on male reproductive organs included small or soft testis and epididymis in some studies (OECD TG 422, p-cymene, Study report, 2019; OECD TG 415, cyclamal, Study report, 2011a), decrease in testis and epididymis weight in most studies, and decrease in levator ani-bulbocavernosus muscle weight (OECD TG 422, p-cymene, Study report, 2019) and seminal vesicle weight (OECD TG 408, cyclamal, Study report, 2020b), seminal vesicles and prostate (14-day study, 3-(p cumenyl)propionaldehyde, Study report A). Testicular atrophy (atrophy of seminiferous tubules) (OECD TG 422, p-cymene, Study report, 2019) or atrophy of testis, epididymis and seminal vesicle (14-day study, 3-(p-cumenyl)propionaldehyde, Study report A) were also described. Histologic examination revealed testicular degeneration, depletion or retention of germinal epithelium (OECD TG 422, p-cymene, Study report, 2019) and presence of interstitial inflammatory cells, apoptotic epithelial cells, degenerate spermatogenic cells in the ducts, epithelial hyaline droplets, decreased number of spermatozoa (Natsch et al., 2021). Presence of luminal cell debris in seminiferous tubules and cribriform change in epididymis was described for p-cymene (OECD TG 422, p-cymene, Study report, 2019). For most of these effects a dose and time dependent increase in incidence and severity could be observed.

Sperm parameters were affected in all rat studies (except for the 14-day p-cymene study (Study report, 2018), which did not investigated sperm parameters) and consisted mainly of reduced sperm and/or spermatocyte numbers, reduced sperm motility and increased

number of sperms with abnormal morphology (i.e. detached heads, no heads, abnormal neck, coiled tail). These effects mostly showed a dose dependent increase in incidence and severity. Where investigated, the adverse male fertility was considerably reduced and complete infertility was observed at higher doses. In the OECD TG 422 study with p-cymene (Study report, 2019) there were no pregnancies at the top dose (200 mg/kg bw/d) and reduced number of pregnancies at the mid dose (100 mg/kg bw/d) and in the OECD TG 415 study with cyclamal (Study report, 2011a) fertility index of treated males mated with untreated females was 92%, 100%, 87.5% and 4.3% in control, low-, mid- and top dose group, respectively (0 / 25 / 75 / 150 mg/kg bw/d).

Despite the fact that the different studies had rather different study designs, with the consequence that not all parameters were consistently covered for all members of the cyclamal group and though the wording used in the different studies to describe the microscopic changes differed considerably (e.g. germinal cell depletion vs apoptotic epithelial cells or degenerate spermatogenic cells in the ducts), consistent adverse changes were seen in male reproductive organs and sperm parameters across the different studies, where investigated.

The available studies differ in their design and not all parameters were evaluated for each compound, but the majority of the effects listed above was consistently seen across the studies carried out with the different compounds.

In some studies, **female reproductive organs** were also affected at high dose, including decrease in ovary and uterus weights (cyclamal, OECD TG 415, Study report, 2011a; 14-day study, Study report, 2018), changes in cyclicity (p-cymene, OECD TG 422, Study report, 2019) and effects on female fertility in the cross-over trial (cyclamal, OECD TG 415, Study report, 2011a), where cyclamal treated females mated with untreated males had reduced number of implantation sites and increased pup mortality at the top dose. Increase in pre-implantation loss was also seen with p-cymene (OECD TG 422, Study report, 2019).

Two 14-day studies were also conducted in **rabbits**, one with cyclamal (Study report, 2011b) and the other with 3-(p-cumenyl)propionaldehyde = cyclemax (Study report B).

In the cyclamal study there were no effects on morphology or weight of male reproductive organs, but there was a dose related decreasing trend of mean number of motile sperm and total sperm count (ejaculated samples) in the absence of adverse general toxicity. RAC acknowledges that there was large variation within the measured sperm parameters and as there were only five animals per group included in these sperm investigations, these results are not considered very strong evidence. Further details of this study are discussed in section “Comments received during consultation”.

In the study with cyclemax, all top dose males were affected by macroscopic findings in testes and epididymides, there was increase in residual bodies in testes and in 3/5 animals

there was minimal to mild depletion of spermatozoa in epididymides, 2/5 had detachment of seminiferous tubules of the testes.

It can be concluded that also in rabbits, effects on male reproductive organs were reported, though it appears that the rabbits are less sensitive than rats for this type of effects. It is, however, noted that hardly any general toxicity was seen up to the top dose of 300 mg/kg bw/d in both studies and higher doses could have been tested, with possibly more severe effects on male reproductive organs and spermatogenesis.

In most studies the above-described effects on sexual function and fertility were seen at doses without general toxicity or without marked toxicity. In some studies, there was considerable general toxicity at higher doses (including lethality, considerable weight loss, adverse effects on liver and kidneys).

Table 3 compares the available studies and indicates where effects on male reproductive organs / spermatogenesis and / or fertility were observed, whether the effects were considered slight or severe (incidence and/or severity) and whether these effects occurred in the absence or presence of (severe) general toxicity. The table starts with the studies with the longest duration, with the studies of shortest duration at the lower end of the table. The exact doses used in the studies cannot be directly compared, due to the different molecular weights of the substances, but it allows a rough estimate and comparison of the doses leading to effects. It can be concluded that effects were mostly recorded in the absence of severe general toxicity or total absence of general toxicity, the longer the duration of exposure, the lower the dose needed to induce an effect and that rats seem to be more sensitive towards the investigated effects than rabbits.

***Table 3**: Comparison of the results of the different studies relevant for sexual function and fertility*

Dose: mg/kg bw/day	10/15	25/30	50	75	100	120	150	200	250	300	500
Cyclamal, OECD 415 (Study report, 2011a), rat ##											
General tox					F:X			M:X**			
Male repro organs /sperm-parameters, fertility		X			X			X			
Cyclamal, OECD 408 (Study report, 2020b), rat											
General tox		(X)				(X)					
Male repro organs /sperm-parameters						X					
p-Cymene, OECD 422 (Study report, 2019), rat #											
General tox					(X)			X§			
Male repro organs /sperm-parameters, fertility			(X)		X			X			
Cyclamal, 28 day (Study report, 2020a), rat											
General tox										(X)	
Male repro organs /sperm-parameters					X					X	
p-Cymene, 14 days (Study report, 2018), rat											
General tox											X§
Male repro organs ***											X*
Cyclamal, 14 day (Study report, 2011b), rabbit											
General tox										(X)	
Sperm-parameters, fertility		(X)			(X)					(X)	
3-(p-Cumenyl)propionaldehyde, 14 days (Study report A), rat											
General tox				(X)					(X)		
Male repro organs /sperm-parameters				X					X		
3-(p-Cumenyl)propionaldehyde, 14 days (Study report B), rabbit											
General tox										(X)	
Male repro organs /sperm-parameters										X	
4-iPBA, 5 days (Natsch et al., 2021), rat											
General tox							(X)				
Male repro organs /sperm-parameters	(X)		(X)				X				

(X) … slight effects; X … clear adverse effects
Coloured fields indicate the doses tested in the specific study, different colors are used for the different substances.
M … males, F … females
… M: exposure for 35 days, F: exposure for 63 days; ## … M: exposure for 134 days, F: exposure for 71 days
§ … 1 female died
* … 1 F also affected: small uterus and cervix (1/3)
** … Females not evaluated at this dose – euthanised on GD 25 – non-pregnant
*** … study did not investigate sperm parameters

No toxicity data are available for 4-isopropyl benzaldehyde; however, based on the read across presented by the DS, and evaluated and supported by RAC (see also RAC general comment), RAC considers the available data sufficient to demonstrate clear evidence for adverse effects on sexual function and fertility for all members of the cyclamal group. The effects were consistently seen across studies and substances tested. There were also some indications for adverse effects on female reproductive organs and fertility, though less consistent, but it is acknowledged that the available studies were partly not designed to assess effects in females (e.g. included only males). The observations made in females are considered supportive evidence.

RAC concludes also that the findings are not considered to be secondary unspecific effects as they were seen in the absence of (marked) general toxicity.

In line with the response to the comments from consultation, provided by DS and RAC (see section on comments received during consultation as well as the RCOM document), RAC is of the view that there is no evidence to conclude that the effects seen in rat as well as rabbit are not relevant to humans.

Therefore, in a weight of evidence approach and considering all the above information, RAC considers the **classification as Repr. 1B; H360F is warranted for all members of the cyclamal group,** based on read across and in alignment with DS proposal.

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Adverse effects on development

The studies relevant for the assessment of adverse effects on development were:

Studies with p-cymene:

- a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422, GLP) in rats by oral gavage

Studies with 3-p-cumenyl-2-methylpropionaldehyde (cyclamal):

- a prenatal developmental toxicity study (OECD TG 414, GLP) in rats by oral gavage

- a one-generation study (OECD TG 415) in rats by oral gavage

p-cymene

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422, GLP; Study Report 2019), Sprague Dawley rats were

administered 0, 50, 100 and 200 mg/kg bw/d p-cymene via oral gavage. This study has already been described in the section on sexual function and fertility.

Findings indicative of an effect on development included a dose-related decrease in the number of litters (9, 9, 4 and 0 at 0, 50, 100 and 200 mg/kg bw/d). As no offspring were produced at the top dose, the remaining parameters could only be assessed in the control, low- and mid-dose groups. A treatment-related increase in pre-implantation loss was reported (1.8%, 5.9% and 7.1% at 0, 50 and 100 mg/kg bw/d, respectively). Post-implantation survival and live birth index were reduced at 100 mg/kg bw/d (87.3% vs 95% in controls and 94.3% vs 100% in controls, respectively) and the number of litters with less than 100% viability was increased at this dose (1/4 litters with 100% viability vs 9/9 in control). Mean pup weights were reduced at the mid dose (-11% in males, -9% in females, no information on statistical significance) on PND 1, but not on PND 4, 7, 11 or 13. Viability indices on PND 4, 7 and 13 were comparable with control in treated animals.

Overall, this study provides evidence of adverse effects on development in rats. The live birth index and post-implantation survival were statistically significantly reduced and average pup weight on PND 1 was statistically significantly lower (-10%) at the mid dose (no pups at the top dose). These effects occurred in the absence of marked general toxicity in the parental animals.

3-p-cumenyl-2-methylpropionaldehyde (cyclamal):

In a prenatal developmental toxicity (OECD TG 414, GLP; Study Report, 2021), Wistar rats (22 females/dose) were administered 0, 25, 75 and 150 mg/kg bw/d of cyclamal via oral gavage during gestation days 6 – 20.

There were no deaths and no clinical signs in the dams. Slightly reduced food intake and slightly lower body weights were observed at the top dose on the first two days of dosing (GD 6 and 7), however food consumption and body weight gains were generally comparable to controls for the rest of the study. Mean absolute liver weights were increased from the mid-dose but without dose-dependence. Hepatocellular single-cell necrosis was reported in all treated groups, and was described as minimal, perivascular and/or random. Decreases in T3 and T4 levels was seen from the mid-dose, whereas an increase in TSH was only seen at the low dose.

The number of corpora lutea was increased in treated groups compared to controls (11.5, 12.3*, 12.6 and 12.8* at 0, 25, 75 and 150 mg/kg bw/d, where *p≤0.05). Intrauterine survival was not affected by treatment. Mean foetal body weights were reduced from the mid-dose (mid-dose: -4% to -6% (p≤0.05); top dose: -8.5% to 9.5% (p≤0.01)). The values were stated to be below the historical control data (HCD) range of the laboratory, although the HCD were not available for review. There were no other relevant findings in the offspring.

RAC noted that the applied doses did not induce any meaningful toxicity and considered that higher doses could have been tested in the study. Despite the low doses, a statistically significant reduction in foetus weight was seen from the mid-dose, outside of the HCD.

In a one-generation reproduction toxicity study (OECD TG 415, GLP; Study Report 2011a), Sprague Dawley rats were administered doses of 0, 25, 75 and 150 mg/kg bw/d cyclamal via oral gavage. A detailed description of the study is presented under the section on “sexual function and fertility”, including details regarding the effects on parental animals.

When treated males were mated with untreated females, no offspring were produced at the top dose (i.e., owing to infertility of the males treated with 150 mg/kg bw/d). In the other treated groups, lower relative brain weight was reported in the pups (-6% at both the low and mid dose).

When untreated males were mated with treated females, pregnancy occurred in 25 (100%), 24 (96%), 24 (96%) and 24 (96%) dams at 0, 25, 75 and 150 mg/kg bw/d, respectively. A decrease in implantation sites was seen at the top dose (-11%) and the number of dams with all pups dying between PND 1 and 5 was increased (16.7% vs 0% in control). The number of pups delivered per litter (-15%), number of liveborn pups/litter (-17%) and the number of stillborn pups/litter (2.7% vs 0% in control) were also affected at this dose. Pup mortality was increased at the low (4 vs 0 days 12–15) and top dose (18 vs 1 day 1, 51 vs 12 days 2-5), and pup viability index was reduced at the top dose (75.7% vs 96.3%). Viability index was also decreased at the mid dose, but the finding was not statistically significant. Survival of pups was further decreased at the top dose until day 22 (number of surviving pups/litter: -17% day 1, -36% day 22; live litter size: -18% day 1, -23% day 22).

Mean pup body weight per litter was statistically significantly decreased from the mid-dose. For the mid-dose, these values ranged from -10% on PND 1 to -13% on PND 22 and in the top dose from -11% on PND 1 to -14% on PND 22. The average pup body weight gain in males of these groups continued to be lower during the entire post-weaning period. Body weight gain was also decreased from the mid-dose (mid dose: -7% days 30-37; top dose: -12% days 23-30 and -9% days 30-37 postpartum), as were mean body weights (mid-dose: from day 23 to 51 ranging from -13% to -6%; top dose ranging from -20% to -8%, days 23-57). Feed consumption was lower in these groups, but when related to body weight, feed consumption was actually higher compered to control. Absolute feed consumption was also reduced in top dose pups (-17%; days 23 to 30 and -8%, days 30-37), while relative feed consumption was increased (at mid-dose ranging from +9% to +5%, days 30-44 and at top dose from +8% to +6%, days 30-57). In female pups, body weight gain was reduced at the mid-dose (-9%, days 23-30), while body weight was

reduced in mid dose (ranging from -12% day 23, to -6% day 51) and top dose (from -18% day 23, to -6% day 51).

Terminal average body weight was 4% (not statistically significant) lower in top dose female pups, compared to controls. Absolute feed consumption was also reduced in top dose pups (-14% days 23 to 30), while relative feed consumption was increased (at mid dose +6% days 23-57 and at top dose +4% days 23-57).

The effects on pup body weight did not lead to a delay in the onset of puberty in either males or females, even though in males the average body weight on the day of preputial separation at the mid and top dose was statistically significantly lower than controls. In male pups, anogenital distance (AGD) was normal on PND 1, but statistically significantly reduced in mid- and top dose group on PND 22. After correlation with the lower body weight seen in this group, the difference to controls was longer apparent. In top dose female pups, a statistically significant increase in AGD on PND 1 was observed after correction for body weight. This effect was no longer apparent on PND 22.

Absolute weight of (left) epididymis was statistically significantly reduced (-10%) in male pups at 150 mg/kg bw/d, as were absolute weights of the pituitary (-17%) and brain (-4%). Absolute adrenal weights were also reduced at mid dose (mid dose: -15%, top dose: -13%). Relative testis weights were statistically significantly increased at the mid- (+5%) and top dose (+6%). In female pups, brain weight was statistically significantly reduced at the mid- (-3%) and top dose (-6%), as were absolute ovary weights in the top dose (-17%).

Lenticular opacity was observed at the top dose (in one or both eyes in one or more pups from 20 out of 24 litters). These effects were first observed on PND 16 and persisted to PND 22 and were confirmed during necropsy (in those pups killed on PND 22). This observation was more prevalent in F1 generation male rats than in female rats (18 males vs 6 females). The finding was reported in one pup in the control group. No other gross lesions were observed in pups that survived until scheduled necropsy on PND 22, except one top dose male pup, which had a tan area on the left kidney. In the pups that were found stillborn, found dead or humanely euthanised, no milk was present in the stomach of 1, 5, 5 and 14 pups at 0, 25, 75 and 150 mg/kg bw/d, respectively. There were no correlations between dams with low body weight and pups found dead.

The following text is copied directly from the RAC opinion and summarises RAC's position on developmental toxicity:

The results of the two studies with cyclamal demonstrate clear evidence for adverse effects on development. In the OECD TG 415 study (Study report, 2011a) there were clear effects on post implantation loss, live born pups, pup survival at birth and up until end of lactation.

Lower birth weight is considered to demonstrate a disadvantage for later development and pup body weights were lower in mid- and top dose, from PND 1 to PND 22 and continued to be lower also in the post weaning period, up until PND 40-50 in mid dose pups and until the end of the study (PND 60) in top dose pups.

In the top dose of the cyclamal study (OECD TG 415, Study report, 2011a), pups developed lenticular opacity, which according to devtox.org1 is classified as malformation. This effect evolved not before PND 16 and persisted up until PND 22 (confirmed at autopsy). Most of the litters were affected and the effect was mostly not reversible in those animals kept until PND 60.

These observations were made in the absence of relevant maternal toxicity and are in line with all four major manifestations of developmental toxicity listed in Annex I, paragraph 3.7.1.4 of the CLP Regulation ((1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency) were observed, as there was reduced survival (increase in post-implantation loss, reduced number of live born pups, reduced pup survival at birth and up until end of lactation), structural abnormality (lenticular opacity), altered growth (lower pup weight, persisting up until the end of the observation period on PND 60) and functional deficiency (lenticular opacity).

Despite the absence of any relevant maternal toxicity in the second study conducted with cyclamal, the only available developmental toxicity study (OECD TG 414, Study report, 2021), there was a slight, but statistically significant reduction of foetal body weight: mid dose: -4% to -6% ($p \leq 0.05$) and top dose: -8.5% to 9.5% ($p \leq 0.01$). No other effects were observed, but it is noted that the OECD TG 414 study does not cover development after birth (potential development of lenticular opacity was only seen on PND 16 and later in the OECD TG 415 study).

Similar effects were also seen in the OECD TG 422 study with p-cymene, but effects were generally slight and mostly not statistically significant, again in the absence of relevant maternal toxicity. Observations included reduced survival and lower body weights. Lenticular opacity was not observed, but as the animals were only observed until PND 13, it is not possible to clarify whether p-cymene would also induce this effect after PND 16 or later, as seen with cyclamal.

For the other members of the cyclamal group, including the common metabolite 4-iPBA, there are no studies available that could inform on potential developmental toxicity of these substances. The DS still proposed to classify all members of the group as Repr. 1B for development, based on read across supported by similar structures, similar toxicokinetics and comparable results in three toxicity studies covering cyclamal and p-cymene.

RAC agrees with the DS that the data available for cyclamal clearly support a classification as Repr. 1B for development and therefore proposes to classify cyclamal as Repr. 1B, H360D. However, RAC considers that the read across is not as well supported for

developmental toxicity as for sexual function and fertility, where all except one group member, including the common metabolite 4-iPBA, were investigated in respective toxicity studies. Therefore, based on the effects seen in the single study with p-cymene (OECD TG 422, Study report, 2019), which are less severe but in line with the observations made for cyclamal, structural similarity as well as similar toxicokinetics, RAC proposes to classify the remaining members of the cyclamal group as Repr. 2; H360d.

RAC further considers the available information from the members of the closely related substances of the bourgeonal group as supportive evidence. RAC notes that despite the distinct difference of the group in para-position (members of the bourgeonal group have an additional methyl-group), the substances are structural similar, have similar toxicokinetics and similar effects on the developing organism as seen for cyclamal (except lenticular opacity) and p-cymene. In their response to comments also the DS supported that read across could in principle be extended to include all members of both groups in one read across. For developmental toxicity, the DS proposed to classify the members of the bourgeonal group as Repr. 2 (in a separate CLH dossier), which is justified by the observed effects on growth and survival together with some maternal toxicity and the harmonised classification as Repr. 2 for development of lysmeral, one of the members of the group.

Classification in Category 2 is supported by the recommendations for read across from the Guidance on the application of the CLP criteria (CLP guidance, ECHA 2017), which states that in cases where there is uncertainty with regard to the robustness of the read across prediction a lower category may be applied.

In conclusion, RAC proposes to classify the members of the **cyclamal group** as **Repr. 2; H360d,** based on read across, with the exception of **cyclamal**, for which RAC proposes to classify as **Repr. 1B; H360D**, based on data for the substance itself.

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Effects on or via lactation

RAC considered that the available data did not support classification for effects on or via lactation. Effects observed in the offspring during the lactation period (e.g., lower body weight, lower survival, development of lenticular opacity) could not be conclusively linked to lactation and could have been a consequence of *in utero* exposure. As such, RAC considered the findings supportive for the classification for developmental effects, rather than evidence for effects on or via lactation.

Classification proposed by the Agency:

The Agency supports the grouping and read-across approach applied by the DS and by RAC.

Adverse effects on sexual function and fertility

There is clear evidence that members of the cyclamal group cause adverse effects on male reproductive organs and spermatogenesis (leading to infertility at high doses) in rats. The rat data also provide evidence of adverse effects on female reproductive organs (e.g., decreased ovary and uterus weights), effects on cyclicity and, in the cross-over trial, where cyclamal-treated females were mated with untreated males, a reduced number of implantation sites and increased pup mortality at the top dose. An increase in pre-implantation loss was also seen with p-cymene. The findings in male and female rats occurred in the absence of severe general toxicity in the parental animals.

The findings in rats are supported by studies in rabbits. In a 14-day study in rabbits with cyclamal, there was a dose-related decreasing trend in the mean number of motile sperm and total sperm in the absence of severe general toxicity. The Agency notes the non-guideline, non-GLP status of this study, the small group sizes (5 animals) and large variations in the sperm parameters.

In a 14-day study in rabbits with cyclemax, all top dose males had microscopic findings in the testes and epididymides. There was an increase in residual bodies in the testes, minimal to mild depletion of spermatozoa in epididymides (3/5), detachment of seminiferous tubules of the testes (2/5) and an increase in abnormal sperm. Again, the Agency notes the non-guideline, non-GLP status of this study and the small group sizes (5 animals). However, taken together, the rabbit studies provide some limited evidence of reproductive toxicity which does not contradict the findings in rats.

The Agency has considered the arguments regarding the mode of action (MoA), adverse outcome pathway (AOP) and human relevance submitted during the EU public consultation. The Agency agrees with the response of the DS and RAC that further information is needed to establish the MoA and AOP, and that based on the available data, human relevance of the adverse effects on reproductive toxicity seen in animal studies cannot be excluded.

Overall, the Agency agrees with RAC's conclusion on the classification – the substances in the cyclamal group warrant classification as **Repr. 1B; H360F (May damage fertility).**

Adverse effects on development

There is clear evidence that cyclamal causes developmental toxicity in rats (post-implantation loss, reduced live born pups, reduced pup survival, malformations (lenticular

opacity)) in the absence of severe maternal toxicity in the parental animals. The human relevance of these findings cannot be excluded, therefore the Agency agrees with RAC's conclusion that cyclamal warrants classification as **Repr. 1B; H360D (May damage the unborn child).**

The Agency agrees with RAC that the read-across is not as well supported for developmental toxicity as it is for sexual function and fertility, and that the remaining members of the cyclamal group warrant classification as **Repr. 2; H361d (Suspected of damaging the unborn child).**

Effects on or via lactation

The Agency agrees with RAC's conclusion – classification for effects on or via lactation is not warranted.

Aspiration hazard

Not assessed in the CLH report or RAC Opinion.

Environmental hazards

Hazardous to the aquatic environment

Not assessed in the CLH report or RAC Opinion.

Other hazards

Hazardous to the ozone layer

Not assessed in the CLH report 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:

Substance name	**Classification**
3-*p*-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal	Repr. 1B; H360FD (May damage fertility. May damage the unborn child)
p-cymene; 1-isopropyl-4-methylbenzene	Repr. 1B; H360Fd (May damage fertility. Suspected of damaging the unborn child)
3-(*p*-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal 4-isopropylbenzaldehyde; cuminic aldehyde 4-isopropylbenzoic acid; cuminic acid	Repr. 1B; H360Fd (May damage fertility. Suspected of damaging the unborn child)

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

n/a

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

References

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/

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: p-cymene; 1-isopropyl-4-methylbenzene; 3-p-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal [1]; 3-(p-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [2]; 4-isopropylbenzaldehyde; cuminic aldehyde [3]; 4-isopropylbenzoic acid; cuminic acid [4] EC Number: 202-796-7; 203-161-7[1]; 231-885-3 [2]; 204-516-9 [3]; 208-642-5 [4] CAS Number: 99-87-6; 103-95-7103-95-7 [1]; 7775-00-0 [2]; 122-03-2 [3]; 536-66-3 [4] CLH-O-0000007585-65-01/F Adopted: 28 November 2024, Published: 27 October 2025. Written by Kemi (Swedish Chemicals Agency). Accessed February 2026.

ECHA (2025) Committee for Risk Assessment (RAC) Opinion (including Annexes) proposing harmonised classification and labelling at EU level of p-cymene; 1-isopropyl-4-methylbenzene 3-p-cumenyl-2-methylpropionaldehyde; 2-methyl-3-(4-isopropylphenyl)propanal 3-(p-cumenyl)propionaldehyde; 3-(4-isopropylphenyl)propanal [1] 4-isopropylbenzaldehyde; cuminic aldehyde [2] 4-isopropylbenzoic acid; cuminic acid [3] EC Number: 202-796-7; 203-161-7; 231-885-3 [1] 204-516-9 [2] 208-642-5 [3] CAS Number: 99-87-6; 103-95-7; 7775-00-0 [1] 122-03-2 [2] 536-66-3 [3]. Document ref: CLH-O-0000007585-65-01/F. Adopted: 28 November 2024, Published: 27 October 2025. Accessed February 2026 and April 2026.

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
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
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
EU	European Union
GLP	Good Laboratory Practice
h	Hours
K_{OC}	Organic carbon-water partition coefficient
K_{OW}	Octanol-water partition coefficient
LC_x	x% lethal effect concentration
MCL	Mandatory Classification and Labelling
M-factor	Multiplying factor
MW	Molecular weight

NOEC	No-observed effect concentration
OECD	Organisation for Economic Co-operation and Development
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
STOT-RE	Specific target organ toxicity – repeated exposure
STOT-SE	Specific target organ toxicity – single exposure
TG	Test Guideline
US EPA	United States Environmental Protection Agency
wt	Weight
wwt	Wet weight

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