Australian Government
Department of Health, Disability and Ageing
Australian Industrial Chemicals Introduction Scheme

Ethanone, 1-phenyl- (Acetophenone)

Evaluation statement (EVA00191)

1 April 2026

Draft

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AICIS evaluation statement (EVA00191)

Subject of the evaluation

Ethanone, 1-phenyl- (Acetophenone)

Chemical in this evaluation

CAS name	CAS number
Ethanone, 1-phenyl-	98-86-2

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

This evaluation statement includes a human health risk assessment for all identified industrial uses of ethanone, 1-phenyl- (acetophenone).

The use of acetophenone in food is not assessed in this evaluation because this is not considered to be an industrial use under the *Industrial Chemicals Act 2019*.

Summary of evaluation

Summary of introduction, use and end use

There is limited specific information about the introduction, use and end use of the chemical in Australia. The Australian use volume of acetophenone in 2023 was estimated to be 1,000 kg/year based on data collected in the Asia-Pacific region by the International Fragrance Association (IFRA).

Based on international information, the chemical has functional use as a fragrance in a range of products including:

- personal care products (cosmetics)
- cleaning and furniture care products
- laundry and dishwashing products
- air care products.

Typical use concentrations range from 0.002–0.09% with a maximum use concentration up to 0.2% identified.

Acetophenone is also found in other domestic and commercial products including:

- paints and coatings (including thinners and removers)
- lubricants and greases
- adhesives and sealants.

No information on the functional use and concentration in these products has been identified. The chemical is listed as a designated solvent in the *Poisons Standard – The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP 2026).

Acetophenone has various site-limited applications with functional uses as an intermediate, solvent, catalyst and corrosion inhibitor.

Human health

Summary of health hazards

The identified health hazards are based on the available data for the chemical. There are no studies investigating the absorption and distribution of acetophenone. However, given the physiochemical properties of acetophenone, it is expected to be well absorbed via all routes of exposure. Based on the available data, the chemical:

- has low acute, oral and dermal toxicity
- is, at most, slightly irritating to skin and eyes
- is not likely to be a skin sensitiser
- is not likely to be genotoxic.

Acetophenone is expected to cause narcotic effects after a single exposure, based on observations from acute oral toxicity studies in rats. Observations of narcosis were characterised by clinical signs including wobbly gait, decreased motility, inhibition of turn-around reflex and prostration. Narcotic effects observed in repeat dose studies were transient in nature and observed shortly after dosing. Therefore, hazard classification for a single exposure rather than repeated exposure, is more appropriate. Other observed general systemic effects in repeated dose studies, including reduced bodyweights and changes to liver and kidneys, occurred mainly at high doses and were not considered severe enough to warrant hazard classification.

Based on the available studies in rats and rabbits, there is clear evidence of specific adverse effects on fertility and foetal development. The chemical caused adverse effects on the parturition process and there was some evidence of delays in sexual maturation in females. The chemical caused adverse effects on offspring viability with increased pre- and post-natal mortality observed. There was clear evidence of effects on foetal weight with reduced pup weights observed in all available studies. Although narcotic effects were observed in the developmental and reproductive studies, these developmental and reproductive effects are not considered secondary to parental toxicity. Analyses of individual animals found no correlation between the observation of narcotic effects and adverse effects.

The effects on parturition were observed at the lowest dose tested (75 mg/kg bw/day) in an Organisation for Economic Cooperation and Development Test Guideline (OECD TG) 443 study. Developmental effects relating to offspring viability and body weights were mainly observed at higher doses with a no observed adverse effect level (NOAEL) of 75 mg/kg bw/day. However, some changes to the hippocampus were observed in first

generation pups exposed to this dose. It is uncertain whether these effects were caused by pre- or post-natal exposures.

No reliable inhalation data are available, and no data are available to evaluate carcinogenicity.

For further details of the health hazard information see **Supporting Information**.

Hazard classifications relevant for worker health and safety

This chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

The chemical is already listed in the HCIS (see **Supporting information**). This evaluation supports removal of an acute toxicity and eye irritation classification and addition of the classifications below.

Health hazards	Hazard category	Hazard statement
Specific target organ toxicity (single exposure)	STOT Single Exp. 3	H336: May cause drowsiness or dizziness
Reproductive toxicity	Repr. 1B	H360FD: May damage fertility; May damage the unborn child

Summary of health risk

Public

There is potentially widespread public exposure to acetophenone in various types of cosmetic and domestic products when used as a fragrance at low concentrations.

The chemical may cause adverse effects on fertility and foetal development. A margin of exposure (MOE) methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. Based on the worst-case scenario estimates that assume the chemical is present in all products used daily, at typical use concentrations for the chemical, an MOE of 728 was calculated. MOE values for single products were all > 3000. In addition, a separate MOE of > 1,300 was calculated for use in baby products. For this risk characterisation, an MOE value greater than or equal to 300 is considered acceptable to account for intra- and inter-species differences and extrapolation from a lowest observed adverse effect level (LOAEL) value. This indicates that acetophenone is unlikely to pose a risk to human health if used in cosmetic and domestic products at low concentrations as a fragrance.

The chemical may be used in other consumer products such as paints and paint removers with functional uses other than as a fragrance. Although exact functional uses have not been identified, it is noted that the chemical is listed as a designated solvent in the Poisons Standard and therefore may have use as a solvent in these products. The concentration in these products is unknown but are likely higher than when used as a fragrance. Risk estimates indicate that the chemical would need to be at low concentrations (less than or equal to 0.1%) in paints and paint removers to result in an MOE > 300. Therefore,

concentrations likely to be in use in paints and paint removers (except when present as a fragrance) would result in MOE values significantly below 300. The chemical is currently listed in Schedule 5 of the Poisons Standard if present at > 25% (as itself or in combination with other solvents). No warning statements apply to consumer products containing the chemical at any concentration.

Overall, there is a potential risk if the chemical is used in domestic products with functional uses other than as a fragrance. The risk could be managed by amending the entry in the Poisons Standard.

Workers

During product formulation and packaging, dermal, inhalation and ocular exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical acute and long-term systemic health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk**).

The data available, including overseas exposure standards, indicate that a workplace exposure limit may be beneficial to mitigate the risk to workers. Exposure to the chemical causes narcotic effects and adverse effects on fertility and development in animals. Internationally, exposure standards have been established, although these did not consider more recently available studies on reproduction and developmental toxicity.

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling amends the entry in the Poisons Standard. It is recommended that to manage the potential risk associated with the use of the chemical that the entry:

- restricts the concentration and/or functional use of the chemical in cosmetic and domestic products.

Consideration should be given to the following:

- The chemical has widespread functional use as a fragrance at low concentrations. The chemical is unlikely to pose a risk from this functional use.
- The chemical is listed as a designated solvent and may be used in domestic products such as paints and paint removers.
- Concentrations likely to be in use in paints and paint removers (except when present as a fragrance) would result in MOE values significantly below 300 (and therefore pose a risk to human health).

- Adverse effects on the development of the unborn child can occur from acute exposures.

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety (see **Summary of health hazards** section).

It is recommended that Safe Work Australia consider establishing a workplace exposure limit.

Information relating to safe introduction and use

The information in this statement, including recommended hazard classifications, should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Recommended control measures that could be implemented to manage the risk arising from dermal and inhalation exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

These control measures may need to be supplemented with conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

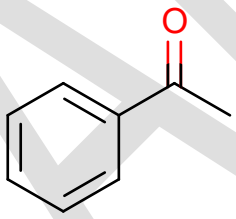
The Executive Director proposes to be satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.
2. A person introducing this chemical should be aware of their obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	98-86-2
CAS name	Ethanone, 1-phenyl-
Molecular formula	C_8H_8O
Associated names	Acetophenone
	1-Phenylethanone
	Acetylbenzene
	Methyl phenyl ketone
Molecular weight (g/mol)	120.15
SMILES (canonical)	O=C(C=1C=CC=CC1)C
Structural formula	

Relevant physical and chemical properties

Physical form	Liquid
Melting point	20°C
Boiling point	202.1°C
Vapour pressure	45 Pa at 25°C
Water solubility	6.2 g/L at 25°C
log K_{ow}	1.65 at 20°C

Introduction and use

Australia

There is limited specific information about the introduction, use and end use of the chemical in Australia. The Australian use volume of acetophenone in 2023 was estimated to be 1,000 kg/year based on data collected in the Asia-Pacific region and reported by IFRA (IFRA)

International

Acetophenone has been identified in a range of consumer and professional applications (Api et al. 2025; CDPH 2023; DeLima Associates n.d.; ECHA 2023; EFSA 2016; EWG n.d.; IFRA n.d.; INCI beauty n.d.; Opdyke DLJ 1973; PCPC n.d.; REACH n.d.; US EPA 2006.; US EPA 2020a; US EPA 2020b).

The chemical has functional use as a fragrance in a range of products including personal care products (cosmetics) and domestic products. Limited concentration data are available.

Reported concentrations include:

- Typical concentrations for soap 0.01%, detergent 0.002%, creams and lotions 0.005%, and perfume 0.09% (Opdyke DLJ 1973).
- Max concentrations for soap 0.15%, detergent 0.024%, creams and lotions 0.03%, and perfume 0.2% (Opdyke DLJ 1973).
- Fragrances 0.2%, and detergents and lotions 0.002–0.005% (Meghrazi Ahadi et al. 2024).

Based on an exposure survey in 2024, the Research Institute for Fragrance Materials (RIFM) estimated that the 95th percentile concentration in fine fragrance was 0.015% (Api et al. 2025). RIFM has calculated maximum acceptable concentrations for IFRA product categories based on the RIFM Crème model (see **International regulatory status**).

The chemical is listed in the International Nomenclature of Cosmetic Ingredients (INCI) database (Personal Care Products Council n.d.). Based on online product databases and data submitted to the California Safe Cosmetics Program (CSPC), the chemical is used in a wide range of cosmetic products, predominantly in hair colourant products. The California Department of Public Health (CDPH) reported that acetophenone was an ingredient in 540 cosmetic products in the state, which accounted for 0.5% of all products reported between 2009 and 2022 (CDPH 2023). Among these, acetophenone was found in:

- 377 hair colouring products (5.0% of hair colouring products)
- 36 hair care products (0.2% of hair care products)
- 32 skin care products (< 0.1% of skin care products)
- 26 hygiene and miscellaneous products (0.3% of personal care products)
- 20 fragrance products (< 0.1% of fragrance products)
- 17 bath products (< 0.1% of bath products)
- 16 baby products (3.7% of all baby products)
- 5 non-permanent make-up products (< 0.1% of non-permanent make-up products)
- 3 sun protecting products (< 0.1% skin-related products)
- 3 shaving products (0.2% of shaving products)
- 1 oral hygiene product (< 0.1% of oral hygiene products).

An additional 220 products had been reported by the CSPC in 2025 (CSPC n.d.).

The chemical has reported use in domestic and commercial products, with identified functional use as a fragrance in dishwashing and laundry products, air care products, cleaning products, and automotive products.

Acetophenone is found in paints (including thinners and removers), lubricants and greases, adhesives, fillers, putties, plasters, and modelling clays. The functional use in these products is not known. No concentration information was identified.

The chemical has reported use in site limited applications, with functional use as a corrosion inhibitor in oil and gas drilling, a solvent for plastics and resins manufacture, an intermediate in organic synthesis including as a photosensitiser and as a catalyst in olefin polymerisation.

The chemical has non-industrial use as a flavouring agent. It is also naturally occurring in a wide range of fruit and vegetables.

The chemical was historically used as an anaesthetic and hypnotic in the 19th and 20th centuries with a brand name of Hypnone.

The Asia-Pacific use volume of acetophenone in 2023 was estimated to be 20,000 kg/year based on data collected by IFRA. In the European Union (EU), acetophenone was registered with an annual introduction volume between 10,000–100,000 tonnes under the Registration, Evaluation, Authorisation and Restrictions of Chemicals Regulation (REACH) (REACH n.d.). According to the United States Environmental Protection Agency (US EPA), the nationally aggregated production volume of acetophenone in the United States of America ranged between 50,000 and 500,000 tonnes per year during 2016–2019 (US EPA 2020a; US EPA 2020b). Additionally, acetophenone is listed on the US EPA's High Production Volume (HPV) chemicals list (US EPA 2020c). In Japan, acetophenone was imported/manufactured at a quantity of 2,000–3,000 tonnes during the 2023 fiscal year (NITE n.d.).

Existing Australian regulatory controls

Public

The chemical is listed in the Poisons Standard as follows (TGA 2026).

Schedule 5:

"PHENYL METHYL KETONE except in preparations containing 25% or less of designated Solvents."

Schedule 5 chemicals are labelled with 'Caution' and are described as: "Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label."

The chemical is also included in the SUSMP definition of a designated solvent.

Workers

The chemical is listed on the Hazardous Chemical Information System (HCIS) with the following hazard categories and statements for human health (SWA n.d.):

Health hazards	Hazard category	Hazard statement
Acute toxicity - oral	Acute Tox. 4	H302: Harmful if swallowed
Eye irritation	Eye Irrit. 2	H319: Causes serious eye irritation

No specific exposure standards are available for the chemical in Australia (SWA n.d.).

International regulatory status

Exposure standards

The following exposure standards were identified (AIHA n.d.; Chemwatch n.d.):

- Time weighted average (TWA): 50 mg/m^3 (10 ppm) in Canada, a majority of reporting EU countries, and the US (including the American Conference of Governmental Industrial Hygienists and American Industrial Hygiene Association), 5 mg/m^3 (1 ppm) in Bulgaria, Kazakhstan, Latvia, and Russia, 100 mg/m^3 (20 ppm) in Romania.
- Short-term Exposure Limit (STEL): 5 mg/m^3 (1 ppm) in Bulgaria, 100 mg/m^3 (20 ppm) in Denmark and Poland.

The following protective action criteria (PAC) (formerly known as temporary emergency exposure limits (TEELs) have been recommended by the US Department of Energy (Chemwatch n.d.):

- 147 mg/m^3 (PAC-1)
- 1622 mg/m^3 (PAC-2)
- 9828 mg/m^3 (PAC-3).

European Union

The European Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) issued, in March 2025, an opinion recommending, among others, a classification for acetophenone as ‘Reprotoxic of Category 1B (H360FD)’. Following the RAC opinion, the European Commission may propose a classification for acetophenone as a ‘Repr.1B’ (CLP Regulation Annex VI entry). According to Article 15(2) of the Cosmetics Regulation, ‘The use in cosmetic products of substances classified as carcinogenic, mutagenic, and reprotoxic (CMR) substances of category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008 shall be prohibited.’ In view of this, regulatory measures must be adopted by the Commission services of the classification as CMR 1A or 1B of the substance(s) concerned in Part 3 of Annex VI to Regulation (EC) No 1272/2008.

Other

The chemical is not included in the IFRA Standard (IFRA n.d.). RIFM has calculated maximum acceptable concentrations for IFRA product categories, which range from 0.0066–0.099% in leave-on personal care products (except fine fragrances), 0.25% in fine fragrances, 0.059–0.43% in rinse-off personal care products, and 0.22–10% in household products (Api et al. 2025).

Human exposure

Workers

The primary routes of exposure during production and use are inhalation and dermal. No exposure studies during typical manufacturing and use were found in peer-reviewed literature.

Public

As acetophenone is used in a wide range of personal care and domestic products (see **Introduction and use**), public exposure to the chemical is expected to be significant. Oral, dermal and inhalation exposure is expected, depending on the type of product. Dermal exposure may be limited to specific areas of the body or may be more extensive depending on the type of product. The duration of exposure for various products is expected to differ significantly as the chemical is used in both rinse-off and leave-on products. For rinse-off products such as soaps or shampoos, exposure might only be for a few minutes, although some residual product can remain. Whereas for leave-on products, the period of exposure could last for several hours. Australian use patterns for the various product categories are assumed to be similar to those internationally.

Chronic exposures – frequently used products

Cosmetic products

Adult dermal exposure to the chemical in cosmetic products (see **Table 1** for details) was calculated as an internal dose (systemic exposure dose) which is proportional to the:

- use volumes (product amounts)
- product retention factors (reflecting proportions of product remaining on the skin during normal use)
- dermal absorption of the chemical.

For the exposure assessment, the use volumes and product retention factors were determined using values previously established by the Scientific Committee on Consumer Safety (SCCS 2023). Product categories were chosen based on typical identified uses of the chemical. Concentrations were chosen based on reported usual concentrations for soap, detergent, creams and lotions and perfume (see **Introduction and use** section). Although the source for this data was older, the perfume information was of the same order of magnitude as recent estimated use concentrations for fine fragrances (Api et al. 2025). Therefore, these concentrations are still considered relevant. Where a direct correlation with a reported category was not identified, the concentration in fine fragrances was used as a worst-case scenario. A dermal absorption (DA) rate of 100% is assumed and a default body weight of 60 kg is used for calculation purposes.

Table 1 – Daily dermal systemic exposure to acetophenone through relevant cosmetic products based on the typical concentrations of acetophenone

Product type	Amount (mg/day)	C (%)	Rf (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.005	1	0.0065
Face cream	1,540	0.005	1	0.0013
Hand cream	2,160	0.005	1	0.0018
Fine fragrances	750	0.09	1	0.011
Deodorant (non-spray)	1,500	0.09	1	0.023
Shampoo	10,460	0.01	0.01	0.0002
Shower gel	18,670	0.01	0.01	0.0003
Hand wash soap	20,000	0.01	0.01	0.0003
Hair styling products	4,000	0.09	0.1	0.006
Hair dye products	11,600	0.09	0.1	0.017
Total	–	–	–	**0.067**

Daily systemic exposure = (amount × C × RF × DA)/BW with DA = 100% and BW = 60 kg C = chemical concentration; RF = retention factor; DA = dermal absorption; BW = body weight. A conversion factor of 0.001 is to be applied to account for unit conversion.

The chemical may also be used in cosmetic products that would lead to inhalation exposure. Based on probabilistic modelling, RIFM estimated inhalation exposure and total systemic exposure to the chemical to be 0.000067 and 0.00045 mg/kg/day, respectively (Api et al. 2025). These exposure estimates assume 100% absorption via dermal, oral and inhalation routes and consider 25 product categories, including personal care products and air care products. Inhalation contributes approximately 15%, indicating that non-inhalation routes account for ~85% of exposure. Oral exposures to this chemical are expected to be minor, hence dermal exposure is expected be the main contributor to exposure from cosmetic products. The calculated total systemic exposure (0.05 mg/kg bw) (see **Table 1**) covers the worst-case scenario when acetophenone is used daily in all products at typical concentration levels. Therefore, the estimated total systemic exposure from dermal exposures is considered conservative enough to cover both dermal and inhalation exposures.

The chemical has also been identified as having use in baby products (see **Introduction and use** section). Estimates of exposure from relevant cosmetic products in infants and toddlers are detailed in **Table 2**. The calculation uses daily product exposure values (as mg/kg bw/day) previously established by the SCCS (SCCS 2023, SCCS 2024). The concentrations in products are assumed to be the same as for adults.

Table 2 – Daily dermal systemic exposure to acetophenone in infants and toddlers through relevant cosmetic products based on the typical concentration

Product type	Infant (0-0.5 yrs) daily product exposure (mg/kg bw/day)	Infant (0-0.5 yrs) daily systemic exposure (mg/kg bw/day)	Infant (0.5-1 yrs) daily product exposure (mg/kg bw/day)	Infant (0.5-1 yrs) daily systemic exposure (mg/kg bw/day)	Toddler (1-3 yrs) daily product exposure (mg/kg bw/day)	Toddler (1-3 yrs) daily systemic exposure (mg/kg bw/day)
Body lotion	839	0.042	839	0.042	981	0.049
Face cream	53.2	0.0027	44.5	0.0022	42.5	0.0021
Hand cream	74.6	0.0037	62.4	0.0031	59.6	0.0030
Shower gel	7.4	0.00074	7.4	0.00074	9.37	0.00094
Hand soap	7.4	0.00074	7.4	0.00074	9.37	0.00094
Shampoo	4.79	0.00048	4.79	0.00048	4.52	0.00045
Conditioner	0	–	0	–	4.52	0.00045
Total	–	**0.050**	–	**0.049**	–	**0.057**

Daily systemic exposure = daily product exposure (mg/kg bw/day) × C × DA/100. Hair conditioners are not typically used on infants and not marketed for this age group.

Domestic products

The public may also be exposed to the chemical through its identified uses as a fragrance in domestic products (see **Introduction and use** section), including various cleaning, laundry and dishwashing products. Given the low concentration reported to be used in detergents (0.002%), negligible exposure from use in laundry, dishwashing and cleaning products is expected.

Inhalation exposure from the use of air care products was estimated using the ConsExpo web tool v1.2.1 (RIVM n.d.). The assessment applied standard assumptions and exposure parameters as outlined in the Dutch National Institute for Public Health and the Environment (RIVM) Air Fresheners Fact Sheet (RIVM Report 2021), with the exception of adult body weight, which was set at 60 kg.

The following product scenarios and associated inhalation exposure models were selected within the relevant product categories:

1. Instant action air fresheners – volatile substances

   Scenario: Spraying volatile substances by adult users
   Product: Instant air refreshment sprays (aerosol can)
   Category: Home air fresheners

2. Continuous action air fresheners – scented candles

Scenario: Burning scented candles by adult users
Product: Scented candles
Category: Home air fresheners

These scenarios were selected to represent typical consumer use patterns and product types within the air care category. No specific concentration data for the chemical in air care products has been identified. As air care products typically contain chemicals at higher concentrations than fine fragrances, the maximum reported concentration in fine fragrances (0.2%) rather than the typical concentration (0.09%) has been used as a surrogate.

The estimated daily systemic exposure based on these assumptions are:

- 0.011 mg/kg bw/day for instant action air fresheners
- 0.025 mg/kg bw/day for continuous action air fresheners.

Acute exposures – less frequently used products

The chemical also has identified uses in consumer products that are expected to be used less frequently than the above personal care and domestic products. The concentration of the chemicals in these products is unknown but is expected to be higher than when the chemical has functional use as a fragrance. The chemical may have functional use in these products as a solvent. Based on identified end uses (see **Introduction and** use), paints and paint removers were selected for estimates of exposure. This was based on their potential for high solvent content and likely higher exposure due to product volumes used and exposure duration during application.

Inhalation and dermal exposure from the use of paints and paint removers was estimated using the ConsExpo web tool v1.2.1 (RIVM n.d.). The assessment applied standard assumptions and exposure parameters as outlined in the RIVM Paint Product and Do-It-Yourself Products Fact Sheets (RIVM 2007; RIVM 2022), with the exception of adult body weight, which was set at 60 kg.

The following assumptions were used in the estimates for both products:

- Default adult inhalation rate – 20 m^3/day.
- Exposure area – 450 cm^2 (dermal contact assumed to be through the palms of the hand only).

The following product scenarios and associated inhalation and dermal exposure models were selected within the relevant product categories:

Scenario: Application by adult users
Product: High solid paint (25–30% organic solvents)
Category: Brush and roller painting
Models: Inhalation - exposure to vapour – evaporation from increasing area; dermal – direct contact.

Scenario: Application by adult users
Product: High solvent paint (40–50% organic solvents)
Category: Brush and roller painting
Models: Inhalation - exposure to vapour – evaporation from increasing area; dermal – direct contact.

Scenario: Application by adult users
Product: Liquid paint and lacquer remover
Category: Removers
Models: Inhalation - exposure to vapour – evaporation from increasing area; dermal – direct contact.

As specific concentration data for acetophenone in these products are limited, the highest concentrations at which cumulative dermal and inhalation systemic exposures per event resulted in a margin of exposure (MOE) ≤ 300 based on a point of departure (POD) of 75 mg/kg bw/day, were calculated (see **Public risk** section). These concentrations are detailed in **Table 3**.

Table 3 – Inhalation and dermal systemic exposures per event in paints and paint removers at the highest concentration of acetophenone giving an MOE of ≤ 300

Product type	Highest concentration (%) with MOE ≤ 300	Inhalation daily systemic exposure (mg/kg bw/event)	Dermal daily systemic exposure (mg/kg bw/event)	Cumulative daily systemic exposure (mg/kg bw/event)
High solid paint	0.123	0.17	0.074	0.244
High solvent paint	0.062	0.21	0.037	0.247
Liquid paint and lacquer remover	0.025*	0.25	Negligible	0.25

*The estimate for liquid paint and lacquer remover is based on an exposure time of 300 minutes. This covers application, soak-in time, removing the resulting pulp and assumes the user stays in the room the whole time (RIVM 2022). The calculated concentration would change to 0.1% if it is assumed the user is only in the room during application and removal.

Health hazard information

Toxicokinetics

There are no studies investigating the absorption and distribution of acetophenone. However, given the physicochemical properties of acetophenone, it is expected to be well absorbed via all routes of exposure.

Three *in vivo* studies investigating the metabolism of acetophenone are available. These were non-guideline studies that were also not compliant with good laboratory practice (GLP). These studies indicate several metabolic pathways (ECHA 2024).

In 8 Albino rats given 100 mg/kg of intraperitoneal doses of ^{14}C labelled acetophenone, mandelic acid was detected as the major metabolite in urine. Benzoic acid was detected as a metabolite through exhalation (REACH n.d.).

In 3 groups of 5 male rabbits given intraperitoneal doses of acetophenone, *Ortho*-, *para*- and *meta*-hydroxyacetophenone were detected in urine and accounted for 0.5–0.95%, 0.4% and 0.1% of the administered acetophenone, respectively. 1-Phenylethanol was detected and comprised 3.5% of the administered dose (REACH n.d.).

One *in vitro* study investigated the metabolic rates of acetophenone by NADPH-dependent ketone reductase activity located in the cytosols in several organs of rabbit. This metabolic pathway generated 1-phenylethanol in the rabbit (REACH n.d.).

Acute toxicity

Oral

Acetophenone is listed on the HCIS with the following hazard category and statement for human health: Acute toxicity (oral) — Category 4 (H302 – Harmful if swallowed) (SWA n.d.). The available data from reliable studies does not support this classification and is therefore, not warranted. It is recommended that the classification of acute toxicity be removed.

In a non-GLP compliant acute oral toxicity study similar to OECD TG 401, Sprague Dawley (SD) rats (5/sex/dose) were treated with a single dose of acetophenone. The oral median lethal dose (LD50) was 2,081 mg/kg body weight. Reported sublethal signs of toxicity included piloerection, decreased motility and staggering gait (REACH n.d.).

In a non-GLP compliant acute oral toxicity study similar to OECD TG 401, SD rats (5/sex/dose) were treated with a single dose of acetophenone. The LD50 was 2,200 mg/kg bw. Reported sublethal signs of toxicity included staggering gait, inhibition of turn-around reflex, palpebral ptosis, reduced respiratory rate, decreased body weight, flabby appearance (a state of limpness and reduced muscle tone) and cyanotic extremities (REACH n.d).

Mixed values of the LD50 were reported in 4 other studies in rats (740 mg/kg bw in mice, 900, 3,000 and 3,200 mg/kg bw in rats). However, the reliability of these studies was not assignable due to very poor reporting related to purity, dose levels, pathological examination, or results by sex and group (ECHA 2024).

Dermal

Based on the limited available data, acetophenone is likely to have low acute toxicity via the dermal route.

In a non-GLP compliant acute dermal toxicity study similar to OECD TG 402, applied topically at various doses for 24 hours in an occlusive manner SD rats (5/sex/dose). The dermal LD50 was 3,300 mg/kg bw. Reported sublethal signs of toxicity included staggering gait, prostration, inhibition of turn-around reflex, piloerection, lacrimation, palpebral ptosis, loss of weight and cyanosis (REACH n.d).

Inhalation

No reliable data are available to determine the acute toxicity of acetophenone via the inhalation route.

Specific target organ toxicity – single exposure

Narcotic effects

Based on the effects observed in acute oral and dermal toxicity studies, acetophenone is expected to cause transient narcotic effects after acute exposures, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

Signs of narcosis that were reported in acute oral and dermal studies (See **Acute toxicity – oral and dermal**) include:

- wobbly gait
- decreased motility
- inhibition of turn-around reflex
- prostration.

In the oral studies, effects were observed at the lowest dose tested (1,030 mg/kg bw/day and 710 mg/kg bw/day). In the dermal study, effects were observed from 1,820 mg/kg bw/day.

These effects have also been observed in the following studies on acetophenone:

- repeated dose 90 day oral toxicity study in rodents
- pre-natal developmental toxicity studies
- an extended one generation reproductive toxicity study (EOGRTS) with developmental neurotoxicity
- a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test.

The observed narcotic effects were noted shortly after gavage administration and reversed within the day in all the repeated dose toxicity studies (ECHA 2024).

The chemical has been used as a hypnotic and sedative agent in human medicine (ECHA 2024).

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is at most, slightly irritating to skin.

In a non-GLP compliant skin irritation study similar to OECD TG 404 (but with a prolonged exposure time), 6 New Zealand White (NZW) rabbits were treated with acetophenone for 24 hours under occlusive conditions. Observations were recorded at 24 and 72 hours after patch removal. The following mean scores for individual animals were reported based on observations at 24 and 72 hours:

- Erythema (0.33, 0.33, 0, 0, 0, 0)
- Oedema (0.33, 0.33, 0.33, 0 .33, 0, 0).

All signs of erythema and oedema were fully reversible in all animals by 72 hours (REACH n.d).

In a non-GLP compliant skin irritation study similar to OECD TG 404 (but with a prolonged exposure time), 4 NZW rabbits were treated with acetophenone for 24 hours under occlusive conditions. Observations were recorded at 24 and 72 hours after patch removal. The following mean scores for individual animals were reported based on observations at 24 and 72 hours:

- Erythema (0.5, 0.63, 0.5, 0.38)
- Oedema (0, 0.13, 0, 0).

The erythema was not reversible in all animals within 72 hours but had reduced from the 24-hour observation. The oedema was fully reversible in all animals within 72 hours (REACH n.d).

Eye irritation

Acetophenone is listed on the HCIS with the following hazard category and statement for human health: Eye irritation — Category 2 (H319 – Causes serious eye irritation) (SWA n.d.). The available data do not support this classification and is therefore, not warranted. It is recommended that the eye irritation classification be removed.

In a non-GLP compliant eye irritation study similar to OECD TG 405, 0.1 mL of acetophenone was instilled into 1 eye each of 6 NZW rabbits. The eyes were not washed out after instillation and observed at 24, 48, 72 hours and 7 days. The mean scores (based on 24, 48 and, 72 hour observations) for corneal opacity, iritis, conjunctival redness and chemosis were 0 for all animals (REACH n.d.).

In a non-GLP compliant eye irritation study similar to OECD TG 405, 0.1 mL of acetophenone was instilled into 1 eye each of 4 NZW rabbits. The mean scores (based on 24, 48, and 72 hour observations) for corneal opacity, iritis, conjunctival redness and chemosis were 0 for all animals. At the 1-hour observation, discharge and erythema was observed in 4/4 and 2/4 rabbits, respectively. All signs of irritation were reversible in all animals within 24 hours (REACH n.d.).

Sensitisation

Based on the limited available data, the chemical is not likely to be a skin sensitiser.

Skin sensitisation

In a non-GLP compliant non-OECD TG modified Draize test, intradermal induction was performed on Hartley guinea pigs (10) using 1% acetophenone (vehicle not specified). The animals were challenged 14 days later intradermally with acetophenone at 0.25% and epicutaneously at 20%. After challenge, no reactions were reported in any of the animals. (REACH n.d.).

In silico

Acetophenone did not produce a structural alert for protein binding based on the endpoint specific profiling functionality of the OECD Quantitative Structure-Activity Relationship (QSAR) Application Toolbox (OECD QSAR Toolbox) version 4.5. Acetophenone is predicted to be non-sensitising using the knowledge-based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (version 6.3.0) (Lhasa Limited).
Acetophenone is predicted to be non-sensitising using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31.2.82) GHS model (OASIS LMC).

Repeat dose toxicity

Based on the available data, acetophenone is expected to have narcotic effects. Narcotic effects, including decreased spontaneous activity, ataxia and altered gait, were observed in several repeat dose toxicity studies. These effects were supported by data from acute toxicity studies (see **Acute toxicity** section). Many of the narcotic effects observed in the animal studies were transient in nature and observed shortly after dosing. Therefore, hazard classification for single exposure effects rather than repeated exposure is more appropriate (see **Acute toxicity** section).

Other observed systemic effects, including reduced bodyweights and changes to liver and kidneys occurred mainly at high doses and were not severe enough to warrant hazard classification.

Oral

In a GLP-compliant 90 day study conducted in accordance with OECD TG 408, Wistar rats (10/sex/dose) were administered acetophenone (99.67%) by gavage at 0, 125, 250, or 500 mg/kg bw/day; once a day (REACH n.d.).

Spontaneous activity decreased in a dose-dependent manner in mid and high dose males and females by the end of treatment. Salivation increased in the same groups. Transient ataxia was observed in some males and in one high dose female. In the final treatment week, rearing behaviour was also reduced in a dose-dependent manner, likely secondary to reduced spontaneous activity (REACH n.d.).

In males of the high dose group, there was a treatment-related 15% reduction in body weight gain over the duration of treatment. No adverse effects on food consumption were noted; however, there was a transient reduction in high dose males (REACH n.d.).

The following haematological parameters were altered (REACH n.d.):

- Dose-dependent increases in reticulocyte numbers were observed in both sexes. In males, the increases were 33% at the low dose, 51% at the mid dose, and 97% at the high dose. In females, the corresponding increases were 26%, 50%, and 94%. All changes in reticulocyte counts were significant, except for those in the low dose female group.
- Mean corpuscular volume increased by 5% in mid dose females, and at the high dose, it rose by 5% in males and 4% in females.
- A 7% and 5% reduction in red blood cell count, and haemoglobin levels in the female high dose group, respectively.

The following treatment-related histopathological and organ weight findings were observed (REACH n.d.):

- Absolute liver weights increased in both sexes at the mid and high dose levels, with males showing increases of 18% and 26%, respectively, and females showing increases of 20% and 32%, respectively. Relative liver weights also increased, although the magnitude of these changes was not specified.
- Minor hepatocellular hypertrophy was observed across all groups, with males being more affected than females.
- In males, kidney weights increased by 13% at the mid dose and 16% at the high dose levels. In females, relative kidney weight increased by 13% at the mid dose, while absolute kidney weights rose by 17% and 18% at the mid and high-dose levels, respectively.
- Hyaline inclusions were observed in all male dose groups, with significant increases in incidence in mid and high dose groups, associated with α2-microglobulin (α2-microglobulin-mediated nephropathy is not relevant to humans).

The NOAEL was reported to be 125 mg/kg bw/day.

In a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, 10 male and 5 female SD rats were administered the chemical by gavage once daily at 0, 75, 225 or 750 mg/kg bw/day. An additional 10 females/dose were used for the reproductive component of the study (see **Reproductive and Developmental toxicity** section). Males were dosed from 14 days before mating for a total of 28 days. Females were dosed from 14 days before mating to day 3 of lactation, during the premating, mating, gestation and lactation periods (REACH n.d.).

Narcotic or ‘hypnotic’ effects of the chemical were observed through salivation in the middose and wobbly gait in the high dose group. In addition, decreased activity, unkempt appearance, rough coat, pale skin and fewer faeces were observed exclusively in females in the high dose group. Forelimb grip strength and motor activity were decreased in males of the high dose group (ECHA 2023; ECHA 2024).

At the high dose, body weight gain and food consumption decreased by 21% and 41%, respectively, in males on days 0–3 of the pre-mating period but returned towards control values on day 12–16 of the pre-mating period. In females, body weight gain during gestation days (GD) 0–7 was lowered by 39% but returned towards control values on GD 14–20. Food consumption was lowered in the mid and high dose groups by 13% and 44% during days 0–

3 of the pre-mating period but returned towards control values on days 7–12 of the pre-mating period (REACH n.d.).

Haematological changes were observed in the high dose group but none of these were linked to clinical signs and were within the historical control data (HCD). Absolute heart weights in males in the high dose group were decreased. Gross changes were not supported by associated histopathology and, as such, were not considered toxicologically significant. Increased liver weight (both relative and absolute) was observed in females from the mid dose group. In males, only the relative liver weight increased, and this was exclusive to the high dose group. At the high dose, vacuolar changes in hepatocytes were observed in males and females. The levels of total protein and albumin increased significantly from the mid dose. In addition, globulin levels increased at the high dose. These clinical chemistry observations were made in both males and females but were within the HCD range. Relative kidney weight increased in females from the mid dose (kidney weights were not recorded in males). No kidney microscopic findings were considered toxicologically significant to humans (REACH n.d.).

The NOAEL for general toxicity was reported to be 225 mg/kg bw/day.

Similar narcotic effects, reduced bodyweights, and changes to the liver and kidney were observed in a GLP-compliant EOGRTS conducted in accordance with OECD TG 443. The NOAEL for general toxicity in males and females of the P0 and F1 generations was 75 mg/kg bw/day (see **Reproductive and Developmental toxicity** section).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the *in vitro*, *in vivo*, and *in silico* data, the chemical is not likely to be genotoxic Although the chemical was clastogenic in an *in vitro* study it was negative in an *in vivo* study indicating a lack of clastogenicity.

In vitro

Negative results were reported for acetophenone in the following *in vitro* genotoxicity studies (REACH n.d):

- A bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 with and without metabolic activation at concentrations up to 5000 µg/plate.
- A bacterial reverse mutation assay (1976) in *S. typhimurium* strains TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation at concentrations up to 100 µg/plate.
- A bacterial reverse mutation assay similar to OECD TG 471 in *S. typhimurium* strains TA 98, TA 100 and TA 1537 with and without metabolic activation at concentrations up to 360 µg/plate.

- A bacterial reverse mutation assay similar to OECD TG 471 in *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations up to 360 µg/plate.
- A bacterial reverse mutation assay (similar to OECD TG 472) in *Escherichia coli* strains P3110 (pol A+) and P3478 (pol A-) without metabolic activation at concentrations up to 51.5 µg/plate.
- A mammalian gene mutation assay (OECD TG 476) in the thymidine kinase (TK) locus in mouse lymphoma L5178Y cells with and without metabolic activation at concentrations up to 1,200 µg/plate.
- An SOS/umu assay (1991) in *S. typhimurium* strain TA 1535/psK1002 carrying a fused gene umuC'-'lacZ with and without metabolic activation at a concentration of 680.3 µg/plate.

A positive result was reported for acetophenone in the following *in vitro* genotoxicity study (REACH n.d):

- A mammalian chromosome aberration assay (OECD TG 473) in Chinese hamster lung V79 cells with and without metabolic activation at concentrations up to 1100 µg/plate with clastogenicity observed in the presence of metabolic activation at concentrations of 900 µg/mL and higher. No clastogenicity was observed in the absence of the metabolic activation.

In vivo

In a GLP-compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, NMRI mice (5/sex/dose) were treated with acetophenone (cotton seed oil vehicle) via intraperitoneal injection at single doses of 0, 103, 257 or 515 mg/kg bw/day. The incidence of micronuclei formation in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (REACH n.d.).

In silico

No structural alerts for mutagenicity or clastogenicity were observed for acetophenone using the OECD QSAR Toolbox (version 4.5). The chemical was not predicted to be mutagenic using the expert rule-based system, DEREK Nexus (version 6.3.0) (Lhasa Limited)

QSAR modelling using OASIS-TIMES software (version 2.31.2.82) (OASIS LMC) predicted negative results *in vitro* (Ames mutagenicity and chromosomal aberration) and negative results *in vivo* (liver genotoxicity and micronucleus test). However, acetophenone was out of the applicability domain of the model used for these predictions, except in the case of Ames mutagenicity.

Carcinogenicity

No data are available to evaluate carcinogenicity.

Reproductive and development toxicity

Based on the available data, the chemical is expected to cause specific adverse effects on fertility and development, warranting classification (see **Hazard classifications relevant for worker health and safety** section).

There is clear evidence of adverse effects on sexual function and fertility based on observed adverse effects on the parturition process. Classification is also supported by observed effects on sexual maturation in females. There is also clear evidence of adverse developmental effects on offspring viability with pre- and post-natal mortality observed in 2 reproductive studies in rats supported by some evidence of post-implantation loss in pre-natal developmental toxicity studies in rats and rabbits. There is clear evidence of effects on foetal weight with reduced pup weights observed in all available studies.

Although narcotic effects were observed in several studies, developmental and reproductive effects are not considered secondary to maternal toxicity (ECHA 2023; ECHA 2024; ECHA 2025). Analyses of individual animals found no correlation between the observation of narcotic effects and adverse effects.

Sexual function and fertility

In the Combined Repeated Dose Toxicity Study with reproduction/developmental screening (see **Repeat dose toxicity** section), one female from each of the low and high dose groups were euthanised following mating, as they failed to deliver. At the high dose, prolonged parturition was observed in one female. Absolute weight of the epididymides in males of the high dose group was reduced by 9%; however, the effect was considered to be incidental as there were no accompanying microscopic findings (ECHA 2023; ECHA 2024). There were no effects on the following reproductive parameters (ECHA 2023; ECHA 2024):

- corpora lutea counts
- gestation length
- fertility index
- number of implantation sites.

The NOAEL for reproduction was 225 mg/kg bw/day due to prolonged parturition in the high dose group.

In a GLP-compliant EOGRTS conducted in accordance with OECD TG 443, SD rats (24/sex/dose) (the P generation) were administered acetophenone (vehicle: 0.5% carboxymethylcellulose 400–800cPs) with 0.5% Tween 80 by gavage daily at 0, 75, 225 or 500 mg/kg bw/day. At weaning, pups (the F1 generation) were distributed to different cohorts. They were exposed to the same doses of acetophenone as their parents throughout development. Cohorts 1A and 1B of this study were used to assess reproductive performance and Cohorts 2A and 2B were used to assess neurodevelopmental endpoints. Due to insufficient numbers of surviving pups, the high dose group in C1A contained only 10 males, and in C2A there were only 5 animals per sex and group. In the case of C1B and C2B, there were not enough pups to constitute the high dose group. The absence of high dose groups in these cohorts did not significantly impact the usefulness of the study (ECHA 2023; REACH n.d.).

The following exposure periods applied (REACH n.d.):

- P0 males and females: 10 weeks before mating, during mating, until F1 weaning
- F1 males and females: from weaning (post-natal day PND, 22) up to euthanasia
    - 1A: until PND 90–93
    - 1B: until PND 98–100
    - 2A: until PND 76–78
    - 2B: euthanised on PND 22.

In P0 males and females, the narcotic/hypnotic effects of acetophenone were observed through the following clinical signs:

- hypoactivity and/or half-closed eyes (from the mid dose group)
- staggering gait and recumbency (in the high dose group).

In addition to the narcotic/hypnotic effects, burrowing activity and excessive salivation were observed at all doses. Continuous chewing was observed in both sexes at the high dose. In males of the high dose group, loud/abnormal breathing and reflux were sporadically observed. Abdominal size increased in P0 females of the high dose. None of the clinical signs worsened in dams during late gestation or after delivery. Similar clinical observations were made in males and females of the F1 generation (ECHA 2023; ECHA 2024).

Observations of general systemic toxicity in the P generation included (ECHA 2023; REACH n.d.):

- Lower mean body weights in P0 males during the premating period, with reductions of 3%, 5%, and 6% in the low, mid, and high dose groups, respectively. These values trended back towards control values at the end of the premating period. At the end of the treatment period, only males in the high dose group showed a significant decrease in mean body weight of 6% and mean body weight gain of 9%. These reductions were attributed to decreased food consumption in the first week which reversed as treatment progressed.
- P0 females in the high dose group exhibited increased mean body weight and body weight gain during the premating period, reaching up to 8% and 39%, respectively. Between GD 0–14, higher mean body weights persisted with increases reaching 8% in the high dose group. The weight changes in P0 females were not linked to changes in food consumption.
- Increased liver weights (absolute and relative) in both sexes from 225 mg/kg bw/day accompanied by minimal to slight hepatocellular hypertrophy in males and females at all doses.
- Increased kidney weights in both sexes at all doses, accompanied by tubular basophilia, accumulation of hyaline droplets associated with rat specific α2-microglobulin and pelvic dilation in males.
- Increases in spleen weight were observed in females accompanied by brown pigment (minimal to slight) in the spleen in macrophages in both sexes at all doses.
- Hyperkeratosis in the forestomach and oesophagus in both sexes at all doses.

Most clinical pathology and organ weight changes were not considered adverse.

Some changes in haematological parameters, clinical biochemistry and thyroid hormones were observed in the P0 or F1 generations, none of which were significant or had link to clinical signs (ECHA 2023; REACH n.d.).

Similar effects on bodyweight and organ weight changes were observed in the F1 generation.

The NOAEL for general toxicity in males and females of the P and F1 generations was 75 mg/kg bw/day.

The main critical effect observed on fertility was dystocia. In the P generation, a number of dams were prematurely euthanised due to adverse effects on parturition (not starting, or difficulties in delivery). This was observed at all doses although not in a dose-dependent manner (3/23, 1/21 and 3/21 at 0, 75, 225 and 500 mg/kg bw/d, respectively). In addition, in

some dams euthanised between PND1 and PND4 (2 mid-dose and 4 high-dose animals) there was evidence of retained placenta and/or dead foetuses, which supports that the parturition process was not fully completed in these 6 females. Taken together, there was dose related increased incidence of dams with dystocia and/or incomplete delivery (0, 3 (13%), 3 (14%) and 7 (33%) in controls, low, mid and high dose groups respectively). An analysis of individual animal data by ECHA showed no correlation between narcotic effects and dystocia/incomplete delivery (ECHA 2023; ECHA 2024).

There were no effects on the following reproductive parameters (ECHA 2023; ECHA 2024):

- oestrous cycle
- follicle and corpora lutea count
- sperm parameters
- gestation length
- fertility index
- number of implantation sites
- reproductive organ parameters.

The mating index decreased in a dose-dependent manner with values of 100%, 95.7% and 87.5% reported for the low, mid, and high dose groups, respectively. A causal relationship between narcosis and the decrease in the mating index was not identified (ECHA 2023; ECHA 2024, ECHA 2025).

In the high dose F1 generation group, sexual maturation measured by balanopreputial separation in males and vaginal opening in females were delayed by 3 and 3.5 days, respectively. In males, this delay may be attributed to decreased body weight observed in the F1 high-dose males during weaning. Delays in sexual maturation in females were not secondary to any changes in body weight (ECHA 2023; ECHA2024).

The lowest observed adverse effect level (LOAEL) for sexual function and fertility is 75 mg/kg bw/day (lowest dose tested) due to dystocia.

Development

In a GLP-compliant pre-natal developmental toxicity study conducted in accordance with OECD TG 414, pregnant Wistar rats (25 in the low and mid dose groups and 35 in the control and high dose groups) were administered acetophenone by gavage once daily at 0, 125, 300 or 750 mg/kg bw/day on GD 5–19. Dams were euthanised on GD 20 and the foetuses examined (ECHA 2023; REACH n.d.).

No treatment-related mortality was reported. Systemic effects attributed to the hypnotic effect of acetophenone were observed in dams from the mid dose. The hypnotic effects included transient salivation and transiently reduced spontaneous activity. In some cases, this was associated with half closed eyes and dams adopting a prone position. At the highest dose, additional effects such as ataxia, piloerection, fully closed eyes and apathy were observed. In the mid and high dose groups, significantly decreased body weight was recorded between GD 8 and 20, with reductions of up to 8% and 12%, respectively. Between GD 0 and 20, reduced body weight gain and reduced food consumption were recorded in the mid and high dose groups. Specifically, body weight gain decreased by 23% and 37%, and food consumption decreased by 13% and 23%, respectively. Uterus weights were reduced by 14% and 25% and mean adjusted maternal weight was reduced by 7% and 9% in the mid and high dose groups, respectively (ECHA 2023; ECHA 2024).

There was an increasing dose-related trend in early resorptions and post-implantation losses. However, these changes were not statistically significant and at the high dose were mainly driven by 100% post-implantation loss in one single female. Mean foetal weights were reduced by 6% and 15% in the mid and high dose groups, respectively. This led to a corresponding decrease in total litter weight of 14% and 23% in the same groups, respectively. An increase in bilateral pelvic girdle caudal shift was observed in the mid and high dose groups. This was associated with a higher incidence of supernumerary bilateral full 14th thoracolumbar rib. At the high dose, bilateral pelvic girdle caudal shift and full 14th ribs exceeded the dossier's HCD maximum (ECHA 2023; ECHA 2024).

Maternal and developmental NOAELs were set at 125 mg/kg bw/day based on effects on body weight, organ weight and hypnotic effects in dams, and effects on foetal weight and foetal and pup skeletal malformations.

In a GLP-compliant pre-natal developmental toxicity study conducted in accordance with OECD TG 414, pregnant NZW rabbits (22/dose) were administered the chemical by gavage daily at 0, 60, 170 or 500 mg/kg bw/day on GD 6–28. Dams were euthanised on GD 29 and the foetuses examined (ECHA 2023; REACH n.d.).

Two females were aborted and a third was found dead in the high dose group. The cause of death could not be determined at necropsy. In addition, at the high dose, hypnotic effects were indicated by decreased activity, abnormal gait, laboured and shallow breathing and dams lying on their side. Body weight and body weight gain were transiently reduced at all doses with all body weight effects returning towards control values on GD 29. Food consumption was decreased (% not provided) in the mid dose group up to GD 21 and up to GD 24 in the high dose group. At the high dose, late resorptions and total number of resorptions were increased; however, these changes were not statistically significant. At 500 mg/kg bw/day, post-implantation loss was 11.13% (near the upper HCD range). In addition, this excluded a dam with total litter loss. Foetal weights decreased by 9% and 13% in the mid and high dose groups, respectively. The maternal NOAEL was 170 mg/kg bw/day based on treatment-related mortalities at the high dose. The NOAEL for developmental effects was 60 mg/kg bw/day, based on decreased foetal weights (ECHA 2023; ECHA 2024).

In the Combined Repeated Dose Toxicity Study with the reproduction/developmental toxicity screening test (see **Repeat dose toxicity** section), there was a statistically significant increase in the number of stillborn pups (30 v 2 in controls) at the high dose (750 mg/kg bw/day). Six females in the high dose group experienced total litter loss between lactation days 1–4 and were euthansed. In the high dose group, the number of pups that died, were missing and or cannibalised during PND 1–4 increased significantly. As a result, the viability index was significantly reduced at the high dose, reaching only 22.9%.

At the mid dose (225 mg/kg bw/day), the only remarkable effect upon external examination was desquamation on PND 0 and 4. At the high dose, in addition to desquamation, several other effects relating to skin texture and appearance were noted as well as gasping. On PND 1 and 4, pup body weight per litter was significantly decreased at the high dose. Necropsy of the stillborn pups and pups that died during lactation revealed remarkable effects only in the high dose group. Observations included not having milk present in the stomach and dermal hypoplasia. In addition, one stillborn pup was found to have a cleft palate and pups that died were found to have evidence of autolysis, desquamation and scabbing (ECHA 2023; ECHA 2024). The NOAEL for developmental toxicity was 225 mg/kg bw/day due to effects on pup body weight, pup viability and external observations.

In the EOGRTS (see **sexual function and fertility** section) decreased body weights in male and female pups were observed from PND 1, with reductions of 20% in the high dose group

(500 mg/kg bw/day). In female pups, body weights trended toward control values by PND 21 but remained lower than controls. In males, the reduction became more pronounced reaching 23% by PND 21 (ECHA 2023; ECHA 2024).

The first litter check occurred on PND1. The rate of post-implantation loss increased in a dose-dependent manner with values of 20.3%, 24.1%, 29.8% for the low, mid, and high dose groups, respectively. These rates exceeded laboratory HCD in the mid and high dose groups. This resulted in a dose-dependent decrease in the total number of pups delivered and live born pups. There was a dose-dependent decrease in the live birth index with values of 94.4%, 79.6% and 34.1% for the low, mid, and high dose groups, respectively (ECHA 2023; ECHA 2024). There was an increase in the number of pups that died, were missing and or cannibalised during PND 1–4. Three and 11 females in the mid and high dose groups, respectively, experienced total litter loss. The high mortalities resulted viability indexes of 92.9%, 77.7% and 38.1% for the low, mid, and high dose groups, respectively, measured on PND 4. The following observations were made in deceased pups in all dose groups of the F1 generation (ECHA 2023; ECHA 2024):

- absence of milk in the stomach
- autolysis
- partial cannibalism.

Quantitative assessment of pup mortality indicated that most deceased pups were autolysed, with incidences of 23/42 at the mid dose and 79/132 at the high dose. Absence of milk in the stomach was observed in 12/42 pups at the mid dose and 34/132 pups at the high dose. Notably, 8/12 mid dose pups and 33/34 high dose pups lacking milk were already dead at the first check on PND 1. Taken together, these findings support that offspring mortality was not secondary to impaired maternal care (ECHA 2023; ECHA 2024).

The following clinical signs were observed in high dose F1 pups during the lactation period (ECHA 2023; ECHA 2024):

- malformed and or shortened tails
- haematoma/desquamation/scab
- dehydration
- thin appearance
- cold to touch
- hypoactivity.

Of these, only clinical signs related to the skin were observed in the low dose group. In the mid dose, malformed shortened tails and pups being cold to touch were observed in addition to the skin signs.

The NOAEL for developmental toxicity (excluding consideration of neurodevelopmental effects described below) is 75 mg/kg bw/day based on increased post-implantation loss resulting in a decreased number of liveborn pups, decreased offspring viability and decreased PND 1 bodyweight at doses of 225 mg/kg bw/day and above.

In neurodevelopmental investigations, decreases in the auditory startle response were recorded in C2A males and were significant in the high dose group. Morphometric analysis revealed that entire hippocampus thickness was decreased in the C2A male high dose group, absolute brain weight was reduced by 6% in this group. A dose-related decrease in denate gyrus thickness was also noted. No significant decrease in the auditory startle response or alterations to morphometrics were recorded in C2A females and both sexes of

the C2B cohort (although, it is noted that was no high dose group in the C2B cohort) (ECHA 2023; ECHA 2024).

The EOGRTS did not include the developmental immunotoxicity cohort, splenic lymphocyte immunophenotyping was performed in C1A. Absolute counts of splenocytes and lymphocytes (B cells, natural killer (NK)T cells, T cells, helper T cells and cytotoxic T cells) were decreased in C1A males without clear dose-response. Relative counts of NK and B cells decreased and increased, respectively at the mid dose but not in the high dose group. The concurrent control splenocyte count was outside the HCD range, while all treated values were within HCD (ECHA 2023; ECHA 2024).

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation are adverse effects on fertility and developmental toxicity.

Effects on parturition were observed at the lowest dose tested in OECD TG 443 (75 mg/kg bw/day). Developmental effects relating to offspring viability and body weights were mainly observed at higher doses with a NOAEL of 75 mg/kg bw/day established in the EOGRTS. However, some changes to the hippocampus were observed in first generation pups exposed to this dose. It is uncertain whether these effects were caused by pre- or post-natal exposures. Developmental toxicity effects are often triggered by toxicant exposure during brief, highly sensitive developmental windows and therefore are relevant to acute exposures to the chemical.

Accordingly, the POD, the experimentally derived dose where a toxic effect is first observed, for risk characterisation for both acute and chronic exposure is 75 mg/kg bw/day.

Public risk

Chronic exposures – frequently used products

An MOE methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals.

The MOE approach compares estimated human exposure with a toxicological POD, to determine whether a sufficient margin exists to protect against a particular adverse health effect. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, an MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. However, because the POD is based on a LOAEL rather than a NOAEL, an uncertainty factor of 3 has also been included to account for the LOAEL to NOAEL extrapolation. Therefore, for this risk characterisation, an MOE of greater than or equal to 300 is considered acceptable.

There is potentially widespread public exposure to acetophenone as it is present in various types of cosmetic and domestic products (see **Human exposure** section). The calculated MOE values for use of cosmetic and domestic products in adults are provided in Table 4 and Table 5 respectively.

Table 4 – MOE values for acetophenone in cosmetic products

Product type	POD (mg/kg bw/day)	Daily systemic exposure (mg/kg bw/day)	MOE
Body lotion	75	0.0065	119,230
Face cream	75	0.0013	57,692
Hand cream	75	0.0018	41,667
Fine fragrances	75	0.011	6,818
Deodorant (non-spray)	75	0.023	3,261
Shampoo	75	0.0002	375,000
Shower gel	75	0.0003	250,000
Hand wash soap	75	0.0003	250,000
Hair styling products	75	0.006	12,500
Hair dye products	75	0.017	4,412
Aggregate exposure (all cosmetic products)	–	0.067	1,119

Table 5 – MOE values for acetophenone through inhalation exposure in air care products

Product type	POD (mg/kg bw/day)	Daily systemic exposure (mg/kg bw/day)	MOE
Scented candles	75	0.025	3,000
Instant action air freshener	75	0.011	6,818

MOE values for use of individual products containing the chemical are all ≥ 3,000. The worst-case scenario when acetophenone is used daily in all products results in a combined daily systemic exposure of 0.1 mg/kg bw/day for the chemical, accounting for both dermal and inhalation routes. The MOE based on the POD of 75 mg/kg bw/day is 728. International estimates of exposure (Api et al. 2025) indicate that the MOE would likely be significantly higher. The MOE values for infants (0–0.5 yrs), infants (0.5–1 yrs) and toddlers (1–3 yrs) based on use of the chemicals in baby products are 1,491, 1,522 and 1,317 respectively. These risk estimates indicate that acetophenone is unlikely to pose a risk to human health if used in cosmetic and domestic products at low concentrations as a fragrance.

Acute exposures – less frequently used products

The chemical also had identified uses in consumer products that are expected to be used less frequently than the above personal care and domestic products. This includes paints and coatings including paint removers. The concentration of the chemicals is unknown but is expected to be higher than when the chemical has functional use as a fragrance. Risk estimates (see **Human exposure**) indicate that use in paints and paint removers at concentrations > 0.06% and 0.02% respectively could result in MOE < 300. Although there is some uncertainty whether the POD for developmental neurotoxicity relates to pre- or post-natal exposure, even using a NOAEL of 75 mg/kg bw/day for developmental effects caused by pre-natal exposures, concentrations expected to be in use in paints and paint removers would still likely result in MOE significantly below the revised target MOE of 100 (to account for intra- and inter-species differences).

Therefore, there are potential risks to the public for use of the chemical in domestic products such as paints and paint removers (except when present as a fragrance)

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