Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

1-Butanone, 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-

Evaluation statement (EVA00159)

31 March 2025

Draft

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AICIS evaluation statement (EVA00159)

Subject of the evaluation

1-Butanone, 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-

Chemical in this evaluation

CAS name	CAS number
1-Butanone, 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-	119344-86-4

Reason for the evaluation

New information is available about human health risks.

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 the chemical. This evaluation considers all new reproductive and developmental toxicity information and provides a contemporary risk assessment of this endpoint. It also presents published information on previously assessed toxicity information.

The chemical was assessed as a new industrial chemical under Section 23 of the *Industrial Chemicals Notification and Assessment (ICNA) Act 1989*. The assessment report cannot be linked to this report due to confidentiality provisions covered under Section 105 of the *Industrial Chemicals Act 2019*.

Summary of evaluation

Summary of introduction, use and end use

Based on Australian and international use information, the chemical has commercial uses with the function of chemical reaction regulator including in:

- Ink toner and colourant products
- Paints and coatings.

Concentrations typically range from 1–5%.

Although some possible domestic use of the chemical in inks and coatings may be possible, this is not expected to be widespread. Domestic use of the chemical has not been reported in Australia.

The chemical is used in inks for food contact materials internationally.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical and a close structurally related chemical, 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl)-1-butanone (CAS No. 119313-12-1). Available information indicates the chemical is likely to be absorbed via all routes of exposure.

Based on the available data, the chemical:

- has low acute oral and dermal toxicity
- is not irritating to skin and eyes
- is not considered to be a skin sensitiser
- is not considered to have genotoxic potential.

In repeat dose oral toxicity studies the chemical caused effects in the blood, liver and kidney. The severity of the adverse effects or doses at which effects were observed in various organs is not sufficient to warrant hazard classification.

Based on the available data for the chemical and the read across chemical (CAS No. 119313-12-1), the chemical may cause adverse effects on fertility and development, warranting hazard classification. The chemical caused testicular effects in 2 oral rodent toxicity studies in which males were exposed for 28 days. No testicular toxicity or effects on fertility indices were observed in the 1 generation study with the closely structurally related chemical. An increase in early postnatal mortality and reduced pup weight at a dose associated with maternal toxicity were observed in a reproduction/developmental toxicity study (OECD TG 421) with the chemical. Similar effects (stillbirths, early postnatal mortality, decreased pup weight) were observed without marked maternal toxicity in the 1-generation study with closely structurally related chemical.

There are no experimental data available for the chemical on carcinogenicity or inhalation toxicity.

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

Hazard classifications relevant for worker health and safety

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

Health hazards	Hazard category	Hazard statement
Reproductive toxicity	Repr. 1B	H360Df: May damage the unborn child; Suspected of damaging fertility.

Summary of health risk

Public

Based on the available use information, it is unlikely that the public will be exposed to the chemical. Once inks and coatings are cured the chemical is not expected to be available for exposure. Therefore, there are no identified risks to the public that require management. However, if information becomes available indicating the chemical dose have consumer uses, further risk management may be required.

Workers

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

Given the critical systemic long term effects, the chemical could pose a risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented (see **Proposed means for managing risk**).

Once the product is UV cured, the chemical will be chemically reacted with other components and bound to the matrix of the substrates and is not expected to be available for exposure.

Proposed means for managing risk

Inventory listing

The specific requirement to provide information as a term of the Inventory listing should be varied under Section 86 of the Industrial Chemicals Act 2019 to align the specific information requirement with the risk identified and considered in this evaluation statement as follows:

Term of listing	Details

Specific requirements to provide information to the Executive Director under *Section 101* of the *IC Act*	Obligations to provide information apply.
	
	You must tell the Executive Director the volume of introduction, use and end use of the chemical within 20 working days if:
	
	• The chemical is being introduced for consumer end including in ink toner, colourant products, paints and/or coatings, except uses in articles
	• The end use of the chemical has changed or is likely to change from:
	  ○ Ink toner and colourant products
	  ○ Paints and coatings.
	• The amount of the chemical being introduced has increased or is likely to increase (> 10 tonnes).
	• The chemical has begun to be manufactured in Australia.
	• Information has become available to the person as to an adverse effect of the chemical on the environment.

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).

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 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, or 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; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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.

These control measures should 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.

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.

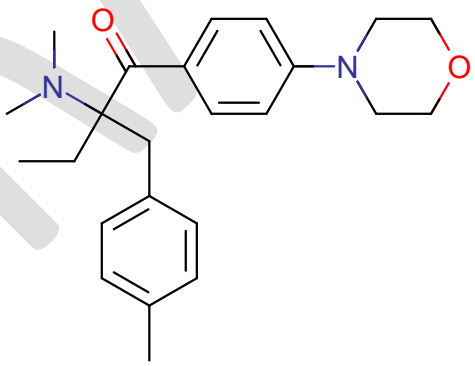
The specific requirement to provide information as a term of the Inventory listing under *Section 101 of the IC Act* assists with managing the risks from introduction of the chemical. The information currently required to be provided is no longer aligned with the risks identified in this evaluation statement. Therefore, a variation to the specific requirement to provide information as a term of the Inventory listing is necessary to manage the risks from introduction of the chemical (see **Proposed means of managing risk**). As this evaluation does not consider environmental risks current information requirements relevant to environmental risks have been maintained.

Note:

1. Obligations to report additional information about hazards under *Section 100 and to provide any information specifically required by the terms of the Inventory listing under Section 101* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	119344-86-4
CAS name	1-Butanone, 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-
Molecular formula	$C_{24}H_{32}N_2O_2$
Associated names	2-(Dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one 2-(4-Methylbenzyl)-2-(dimethylamino)-1-(4-morpholinophenyl)-1-butanone
Molecular weight (g/mol)	380.52
SMILES (canonical)	O=C(C1=CC=C(C=C1)N2CCOCC2)C(N(C)C)(CC3=CC=C(C=C3)C)CC
Structural formula	

Relevant physical and chemical properties

Physical form	Solid powder
Melting point	68°C
Boiling point	>270°C at 101.3 kPa
Vapour pressure	1.3×10^{-10} at 25°C (calculated)
Water solubility	1.9 mg/L at 20°C
pK_a	6.74 ± 0.50 at 25°C
log K_{ow}	4.1 at 20°C

Introduction and use

Australia

Based on Australian information, the chemical has commercial use in inks and coatings at concentrations typically in the range of 1–5%. The chemical was not reported to have domestic use.

International

The chemical has reported commercial uses as a photo initiator in the formulation of UV curable inks, coatings, paint products and photo polymers (REACH n.d.; US EPA 2020). Reported applications include:

- digital printing
- surface coatings
- inks in graphic arts
- electronics (as a photoresist).

Inks containing the chemical may be used to print on polymer, metal, paper, rubber or plastic surfaces before being cured via UV treatment. Typical end use concentrations of the chemical range from 1–5% as reported in publicly available safety data sheets.

The chemical may be used alone or in combination with other photo initiators, including the structurally similar chemical 1-butanone, 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl) (CAS No. 119313-12-1).

Overall, information indicates that the chemical is not likely to be widely available for domestic use. Information from the European Chemicals Agency (ECHA) REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) dossier and the United States Environmental Protection Agency (EPA) did not identify any consumer uses of the chemical (REACH n.d.; US EPA 2016). There is no evidence from available consumer product databases for use of this chemical in such products.

The chemical is used internationally as a photo initiator for inks and colourants used in articles with food contact.

Existing Australian regulatory controls

AICIS

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory) with a specific requirement to provide information as a term of the Inventory listing. This term is published as:

- Specific information requirement: Obligations to provide information apply. You must tell us within 28 days if the circumstances of your importation or manufacture (introduction) are different to those in our assessment.

Under *Section 75(2)(c) of the Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019* the notification obligations under *Subsections 64(1) and (2) of the old law (Industrial Chemicals Notification and Assessment (ICNA) Act 1989 (the ICNA Act))* are taken to be specific information requirements to be provided to the Executive Director.

Specific obligations under *Section 64(1)* applied to the chemical.

Additionally, under *Section 64(2) of the ICNA Act* a person who introduces an industrial chemical that has been assessed under this Act must within 28 days of becoming aware of any of the following circumstances since the assessment, notify the Executive Director in writing:

a) the function or use of the chemical has changed, or is likely to change significantly;
b) the amount of chemical being introduced has increased, or is likely to increase significantly;
c) in the case of a chemical not manufactured, or proposed to be manufactured, in Australia at the time of the assessment – it has begun to be manufactured in Australia;
d) the method of manufacture of the chemical in Australia has changed, or is likely to change, in a way that may result in an increased risk of an adverse effect of the chemical on occupational health and safety, public health or the environment;
e) additional information has become available to the person as to an adverse effect of the chemical on public health, worker health and safety or the environment.

Public

No specific controls have been identified for this chemical.

There are no restrictions or maximum concentration levels for the chemical outlined in the Food Standards Code (FSANZ n.d.).

Workers

The chemical is not listed on the Safe Work Australia Hazardous Chemical Information System (HCIS) (SWA n.d.).

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

International regulatory status

European Union

The chemical is listed on the REACH Candidate List of Substances of Very High Concern (SVHC) for Authorisation, owing to its classification in the hazard class toxic for reproduction and development category 1B, H360Df (ECHA n.d.). In the European Union (EU), companies could have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles.

Other

The chemical is listed in Annex 10 of the Ordinance of the Switzerland Federal Department of Home Affairs on materials and articles intended to come into contact with foodstuffs. The chemical is permitted for use in the production of packaging inks as a photo initiator additive with a Specific Migration Limit (SML) in food of 0.05 mg/kg. The chemical is under re-evaluation (FSVO 2020).

Health hazard information

The chemical 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-1-butanone, (CAS No. 119344-86-4) is structurally similar to chemical 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl)-1-butanone (CAS No. 119313-12-1). The only difference between the structures is that 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-1-butanone (CAS No. 119344-86-4) has an additional methyl group on one of the aromatic rings. They have similar molecular weights and physico-chemical properties. The chemicals have similar toxicological profiles (ECHA 2022). Therefore, data from 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl)-1-butanone has been used as read across for 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-1-butanone (CAS No. 119344-86-4) where required.

Toxicokinetics

No specific toxicokinetic data are available for the chemical.

The available information suggest it is readily absorbed via the oral route based on systemic effects observed in oral studies in rats. Based on the molecular weight (380.52 g/mol), low water solubility (1.9 mg/L), and the partition coefficient (Log Pow = 4.1) absorption via the oral, dermal and inhalation routes is expected. Due to low calculated vapour pressure (1.3×10^{-10}) and high boiling point (>270°C) of the chemical, it is expected to have minimal volatility, with inhalation only likely to arise from processes where dusts or aerosols are produced. The chemical is likely to undergo enzymatic metabolism via the liver.

Acute toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity.

In a GLP compliant acute oral toxicity study conducted in accordance with the Organisation for Economic Cooperation Test Guideline (OECD TG) 423, Wistar Han (HanBrl:WIST) rats (3/sex/dose) were treated with a single dose of the chemical via gavage in polyethylene glycol. The median lethal dose (LD50) was >2000 mg/kg (REACH n.d.).

In a non-guideline acute dose toxicity study, young adult albino rats (3/sex/dose) were administered the chemical via gavage. The LD50 was >2000 mg/kg. Reported sublethal signs of toxicity included transient piloerection, hunched posture, protruding eyes and dyspnoea (REACH n.d.).

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD TG 402, HanBrl:Wist rats (5/sex/dose) had the chemical applied to skin under semi-occlusive conditions for 24 hours. The LD50 was >2000 mg/kg (REACH n.d.).

Inhalation

No data are available. Based on the physicochemical properties, inhalation exposure is not expected unless dusts or aerosols are produced.

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is not considered to be a skin irritant.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 New Zealand white (NZW) rabbits (1 male, 2 females) were treated with the chemical for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48 and 72 hours after patch removal. Mean scores for erythema and oedema were 0 for each animal. No scores above 0 were attributable to any animal at any time point. Corroborating results were observed in another OECD TG 404 study conducted under occlusive conditions (REACH n.d.).

Eye irritation

Based on the available data, the chemical is considered to be at most a slight eye irritant.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, the chemical was instilled into the conjunctival sac of one eye each of 3 NZW rabbits (1 male, 2 females). The eyes were not washed. Observations occurred at 1, 24, 48 and 72 hours following application. Mean scores (based on observations at 24, 48 and 72 hours) for animal 1 were: corneal opacity 0/4, iritis 0/2, conjunctival redness 0/3 and chemosis 0/4. Mean scores for animal 2 were: corneal opacity 0/4, iritis 0/2, conjunctival redness 0.67/3 and chemosis 0.33/4. Mean scores for animal 3 were: corneal opacity 0/4, iritis 0/2, conjunctival redness 0/3 and chemosis 0/4. Slight conjunctival redness, slight conjunctival swelling and slight to moderate reddening of sclera was observed in all animals at the 1 hour time point but were fully resolved within 48 hours (REACH n.d.).

In a similar study in NZW rabbits, conducted according to OECD TG 405, the following mean scores were reported for the 3 animals across 24, 48 and 72 hours: corneal opacity 0/4, iritis 0.11/2, conjunctival redness 0.88/3 and chemosis 0.44/4. Individual animal scores were not reported. At the 1 hour observation time point, slight effects on the iris, slight to moderate conjunctival redness, and slight to moderate conjunctival swelling were observed in all animals. All effects resolved by the 72 hour time point (REACH n.d.).

Sensitisation

Skin sensitisation

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

In a guinea pig maximisation test (GPMT) conducted according to OECD TG 406, intradermal induction was performed on 10 female Himalayan spotted guinea pigs using the chemical at 10% in polyethylene glycol. Topical induction was performed with the chemical at 50% (after pre-treatment with 10% sodium lauryl sulfate). The animals were challenged with the chemical at 50% in polyethylene glycol. After challenge, no reactions were reported in any of the animals (REACH n.d.).

The chemical has no structural alerts for protein binding based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure Activity Relationship (QSAR) Application Toolbox (OECD QSAR Toolbox v4.5).

Repeat dose toxicity

Oral

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure. The severity of the adverse effects or doses at which effects were observed in various organs is not sufficient to warrant hazard classification. In a GLP compliant 28 day study conducted in accordance with OECD TG 407, HanBrl:WIST rats (5/sex/dose – 15, 50 150 mg/kg bw/day; 10/sex/dose – 0 and 450 mg/kg bw/day) were administered the chemical (in polyethylene glycol) via gavage at doses of 0, 15, 50, 150 and 450 mg/kg bw/day 7 days/week. The no observed adverse effect level (NOAEL) was reported to be 50 mg/kg bw/day for the chemical, based on effects at the higher dose levels (150 and 450 mg/kg bw/day).

Effects at 150 mg/kg bw/day included increased relative liver weights in males and females (16 and 15%, respectively) with no associated histopathological changes. There were also tubular hyaline changes in the kidneys of males at this dose and the highest dose. The observed kidney changes in males may be related to the male rat specific phenomenon of alpha 2u-globulin nephropathy. Although special staining was not performed, this is supported by the lack of kidney changes in female rats.

At 450 mg/kg bw day, the highest dose tested, body weights of males and females were reduced by 11% and 14%, respectively. Effects on liver weights were more pronounced than in the 150 mg/kg bw day group, with relative increases of 29% in males and 61% in females. In females, there was slightly increased centrilobular hypertrophy of liver cells without effects on liver enzymes, and a slight increase in alveolar foam cells in the lungs. Slight atrophy of the fatty tissue in bone marrow occurred in both males and females. Slight anaemia was observed in males with a reduction in haematocrit and haemoglobin. Additionally, increased

haematopoietic activity was observed in the spleen of males (this was also observed at the lower dose levels of 50 and 150 mg/kg bw day). These haematopoietic changes were associated with a compensatory mechanism for reduced haemoglobin and haematocrit levels and increased proportion of reticulocytes in peripheral blood (ECHA 2022; REACH n.d.).

Effects on the male reproductive system occurred at 450 mg/kg bw/day (see **Reproductive and development toxicity**).

In a GLP compliant reproduction/developmental toxicity screening test (OECD TG 421), Wistar Han rats (10/sex/group) were administered the chemical (in polyethylene glycol) via gavage at 0, 20, 60 or 200 mg/kg bw/day. The total duration of dosing was 28 days in males and 42–52 days in females. The selected dosages were based on a 14 day dose range finding study in females where adverse clinical signs (hunched posture, piloerection), reductions in body weight, liver weight increases and reduced food consumption were observed at 300 mg/kg bw/day.

At 200 mg/kg bw/day, female parental animals displayed transient clinical signs after dosing such as piloerection and hunched posture. One female showed lethargy and pallor. There was reduced food consumption in the first week of dosing and also during lactation in females at the highest dose. Transient body weight loss occurred during the first week of dosing in females at the highest dose. For males there was reduced body weight gain and terminal body weights at 60 and 200 mg/kg bw/day.

Histopathological examination showed glomerular and tubular necrosis of the kidneys with multiple reddish foci in one female at 200 mg/kg bw/day. At the same dose, 2 females had gelatinous and reduced thymus size, with lymphoid atrophy. The 2 affected females also had total litter loss (see **Reproductive and development toxicity**). The NOAEL for systemic toxicity was reported at 60 mg/kg bw/day due to effects on body weights, organs, clinical signs and gross pathology observed at 200 mg/kg bw/day (ECHA RAC 2022; REACH n.d.).

In a 14 day dose range finding study in female Wistar Han rats (4/dose), the chemical (96.4% purity) (in polyethylene glycol) was administered via gavage at 0, 150 or 300 mg/kg bw/day, daily. Observed clinical signs at both treatment groups included hunched posture, piloerection, and rales. Slight body weight loss in 50% of the animals (mean reductions of 0.5% and 4% for 150 and 300 mg/kg bw day dose groups, respectively), reduced food consumption and increased cholesterol levels were observed in both dose groups. Increased liver and adrenal gland weights occurred predominantly at 300 mg/kg bw/day. A NOAEL was not determined (ECHA RAC 2022; REACH n.d.).

In another 14 day dose range finding study, Sprague Dawley (SD) rats (5/sex/dose) were treated with the chemical at 0, 100, 300 and 3000 mg/kg bw/day, daily. No effects were observed at the 100 mg/kg bw/day. There was a dose dependent reduction in body weight gain and food consumption in the remaining dose groups, slight decreases in haemoglobin and erythrocyte counts, increased cholesterol and alkaline phosphatase levels. There was also an increase in organ weights for the liver and adrenals. At the highest dose tested there was a decrease in testes weight. A NOAEL was not determined (REACH n.d.).

Genotoxicity

Based on the available in vitro data, the chemical is not considered to be genotoxic. Negative results were reported in the following in vitro genotoxicity studies:

- A bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA 98, TA 100, TA 1535 and TA 1537 and *Escherichia coli* WP2 uvrA with and without metabolic activation at concentrations up to 5000 µg/plate (REACH n.d.).
- An in vitro mammalian chromosome aberration assay (OECD TG 473) in Chinese hamster lung V79 cells with and without metabolic activation at concentrations up to 100 µg/mL (REACH n.d.).
- A mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus in Chinese hamster lung cells V79 with and without metabolic activation at concentrations up to 3000 µg/L (REACH n.d.).

In QSAR modelling for genotoxicity the chemical and its expected metabolites from simulated rat liver s9 metabolism had structural alerts for in vivo mutagenicity (micronucleus) based on the mechanistic (and endpoint specific) profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox). One metabolite had an alert for in vitro mutagenicity (Ames test).

The QSAR predictions using OASIS TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31.2) indicate that the chemical was negative for in vitro mutagenicity (Ames), chromosomal aberration and in vivo micronucleus formation. The predictions were within the applicability domain of the genotoxicity models.

Carcinogenicity

No data are available for the chemical. The chemical is not considered to be carcinogenic and has no alert for carcinogenicity (genotoxic and non-genotoxic) based on the molecular structure as profiled by the OECD QSAR Toolbox v4.5 (OECD 2020).

Reproductive and development toxicity

Based on the available data for the chemical and the closely structurally related chemical (CAS No. 119313-12-1), the chemical may cause adverse effects on fertility and development which warrants hazard classification (see **Hazard classifications relevant for worker health and safety**). The chemical caused testicular effects in 2 oral rodent toxicity studies. No evidence of testicular toxicity was reported. No effect on fertility indices were observed in the 1 generation study with the closely structurally related chemical.

An increase in early postnatal mortality and reduced pup weight at a dose associated with maternal toxicity were observed in a reproduction/developmental toxicity study (OECD TG421) with the chemical. Similar effects (stillbirths, early postnatal mortality, decreased pup weight) were observed without marked maternal toxicity in the 1-generation study with closely structurally related chemical.

Reproductive toxicity

2 (dimethylamino) 2 [(4 methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-1-butanone (CAS No. 119344-86-4)

In a GLPcompliant reproduction/developmental toxicity screening test (OECD TG 421) (see **Repeat dose toxicity**), Wistar Han rats (10/sex/group) were administered the chemical (in polyethylene glycol) via gavage at 0, 20, 60 or 200 mg/kg bw/day. All animals were dosed prior to mating (14 days), throughout mating, and until termination for male rats, or throughout gestation and to at least lactation day 3 in female rats. The total duration of dosing was 28 days in males and 42–52 days in females. There was reduced food

consumption in the first week of dosing and also during lactation in females at the highest dose. At the same dose, 2 females had gelatinous and reduced thymus size, with lymphoid atrophy. The 2 affected females also had total litter loss.

At the highest dose tested, there was reduced weight of epididymides in males, with absolute testes weight unaffected. Microscopic findings at this dose included moderate intraluminal cell debris in the epididymides in 8/10 males and slight oligospermia in 4/10 males. Examination of the testes showed germ cell exfoliation into the lumen of the seminiferous tubules (without degeneration) in 9/10 males to varying degrees (minimal to moderate). There was no reduction in fertility indices for males at any dose level, and spermatogenic staging was normal for all males. Reproductive performance was unaffected at any dose level. The NOEL was determined as 60 mg/kg bw/day (ECHA RAC 2022; REACH n.d.).

In the same 28 day study described previously (OECD TG 407) (see **Repeat dose toxicity** section), testicular degeneration was observed at the highest dose tested, as well as reduced spermatogenesis and the presence of round spermatids with a lack of elongated spermatids. These effects were not reversible during the recovery period (14 days). Reduced size and organ weights were also observed for the testes and epididymides. No effects on the male reproductive system were seen at the lower doses, and no effects on female reproductive organs were noted at any dose. The NOAEL for reproductive toxicity was determined to be 150 mg/kg bw day in males (ECHA RAC 2022; REACH n.d.).

Read across: 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl)-1-butanone (CAS No. 119313-12-1)

In a 1 generation study (OECD TG 415), Wistar rats (20/sex/group) were treated with the chemical via gavage at 0, 30, 100 or 300 mg/kg bw/day. Absolute testes weights were slightly increased at 300 mg/kg bw/day (by 7%) and absolute and relative prostate weights were reduced (20% and 15%, respectively). Sperm histopathology parameters were not included in the study. Fertility indices were unaffected at any dose group for males and females (ECHA RAC 2016; REACH n.d.).

In a 28 day study used to inform the dose range for the one generation study, Wistar rats (5/sex/group) were administered 0, 10, 100 or 500 mg/kg bw/day. At the highest dose of 500 mg/kg bw/day, severe clinical effects resulted in cessation of dosing. After a 5 day recovery period, the same animals continued for the remainder of the study at a reduced dose of 250 mg/kg bw/day. Sperm motility, spermatogenesis was unaffected by treatment and there were no histopathological effects observed in the testes or epididymides of treated animals (AICIS 2021; ECHA RAC 2016).

In a 14 day repeated dose study, rats (5/sex/group) were administered 100, 300, 1000 or 3000 mg/kg bw/day of the chemical via gavage. Marked body weight loss resulted in termination of several females in the 2 highest dose groups within several days. Reproductive organ weights were reportedly unaffected at up to 1000 mg/kg bw/day, while testicular weight was decreased at 3000 mg/kg bw/day. Further details on this study were not available. A subsequent 28 day study reported no macroscopic changes or weight changes in reproductive organs at 500 mg/kg bw/day (no histopathology was performed) (ECHA RAC 2016).

Developmental toxicity

1 Butanone, 2 (dimethylamino) 2 [(4 methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]- (CAS No. 119344-86-4)

In the same reproduction/developmental toxicity screening test (OECD TG 421) described above in **Reproductive toxicity**, 2 females in the highest dose group (200 mg/kg bw/day) were euthanised on lactation days 1 and 2 respectively due to total litter loss. These 2 females had effects noted in the kidneys and thymus, and clinical signs such as hunched posture and lethargy. At first litter check, the mortality in all 13 pups was from the first female, and 7/14 mortalities for the litter of the second female. The remaining 7 pups from the second female were deceased or missing by the subsequent day. The ECHA Committee for Risk Assessment (RAC) Opinion concluded that maternal toxicity in at least one of the 2 affected females resulted in pup mortality.

Pup mortality was increased at later days, 12 pups were either deceased or missing (6 and 6, respectively) by termination (postnatal days 5–7). This included 7 pups deceased or missing from the second females litter described previously. For the highest dose group, body weights of the pups were reduced on days 1 and 4 of lactation (reductions of 15% and 20%, respectively).

Due to an increase in early postnatal mortality of pups in the high dose group, the NOAEL for developmental effects was reported as 60 mg/kg bw/day, noting that pup mortality may have been secondary to maternal toxicity in some instances (ECHA RAC 2022; REACH n.d.).

Read across: 1-Butanone, 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl) (CAS No. 119313-12-1)

In the same 1 generation study (OECD TG 415) (see **Reproductive toxicity**), an increased in the number of stillborn pups and postnatal mortality was observed at 300 mg/kg bw day, with significant reductions in viability index of pups (postnatal days 1–4) and reduced body weight of pups by 13% and 21% on postnatal days 1 and 21, respectively. An NOAEL of 100 mg/kg bw day for adverse developmental effects was determined. These effects occurred in the absence of significant maternal toxicity. Maternal effects at the highest doses were limited to increased liver and adrenal weights, green/brown discolouration of the liver and kidneys, and red discolouration of the glandular stomach. A classification of Category 1B; 360D was determined by the RAC (ECHA RAC 2016; ECHA RAC 2022).

Effects on or via lactation

1 Butanone, 2 (dimethylamino) 2 [(4 methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-(CAS No. 119344-86-4)

In the OECD TG 421 study of the chemical, there was increased pup mortality. Necroscopy examinations of deceased pups in the 200 mg/kg bw/day group indicated a lack of milk in the stomach. This is inclusive of pups from the 2 females with total litter loss, potentially arising from maternal toxicity. A number of deceased pups at first litter check may have been stillborn, explaining the lack of milk. However, remaining pups and those that died at later time points potentially had a lack of milk in the stomach as a result of maternal toxicity or developmental toxicity. There is insufficient evidence to classify for effects on or via lactation (ECHA RAC 2022).

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