Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

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

Evaluation statement

14 September 2021

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AICIS Evaluation Statement

Subject of the evaluation

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

Chemical in this evaluation

Name	CAS Registry Number
1-Butanone, 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl)-	119313-12-1

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

A human health risk assessment for all identified uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

There is currently no information about the use and volume of use of the chemical in Australia.

Based on international use information, the chemical has large scale commercial and site-limited uses, including as a process regulator, paint additive, surface coating agent, surface active agent, and a photosensitive substance (e.g. use as a photo-initiator).

The chemical is most commonly used as a component of a product under the trade names Irgacure 369, UV 369, Omnirad 369 and PL-369.

International data suggested that the chemical may be used as a binder in cosmetic products, but no additional details on this use was found and no direct evidence of the chemicals use in cosmetics was found. As the chemical is unstable towards UV light, any cosmetic use would be very limited, for example as an initiator in UV-cured fingernail adhesives.

Although some possible domestic use of the chemical in paints and coatings were identified, this is not expected to be widespread.

Human health

Summary of health hazards

The critical health effects for risk characterisation include systemic long-term effects (developmental toxicity).

Information on toxicokinetics of the chemical is not available. Based on its molecular weight (366.5 g/mol), moderate water solubility (5.9 mg/L at 20°C) and partition coefficient (log Pow = 2.91), there is potential for the chemical to cross biological membranes. If absorbed by the oral route, the chemical is unlikely to undergo hydrolysis in the stomach, but is expected to eventually undergo hepatic metabolic degradation. It can be assumed that the chemical and its possible metabolites circulate in the blood, and could possibly pass through the placental barrier, due to observed toxicity on foetal and newborn rats.

Based on the available data, the chemical has low acute oral (median lethal dose (LD50) >5000 mg/kg body weight (bw)) and acute dermal toxicity (LC50 >2000 mg/kg bw) in rats. No acute inhalation data is available.

Based on studies conducted in rabbits, the chemical is not considered to be a skin irritant. The chemical was found to be slightly irritating to the eyes however, no classification is warranted. In a skin irritation test, no irritation effects were observed for the full duration of the study. In an eye irritation test, slight irritation effects were observed within 1 hour after treatment, and all effects were fully reversible within 24 to 48 hours. No data on respiratory irritation is available.

Based on the available data from a guinea pig maximisation test (GPMT), the chemical is not considered to be a skin sensitiser.

In a 28-day repeated dose toxicity study in rats, the chemical caused changes in haematology and biochemistry parameters at both 100 and 250 mg/kg/day, though the changes were not considered to be adverse at the 100 mg/kg bw/day dose level. Increased liver weights and decreased spleen weights were observed in both dose groups. Greenish discolouration of the kidneys and red-brown discolouration in the liver were observed in some animals from the 250 mg/kg/day dose group, and accompanied by relevant histopathological changes in these organs. There were no adverse effects detected in sperm motility. The study authors reported a no observed adverse effect level (NOAEL) of 100 mg/kg bw/day.

Based on the available data, the chemical is not considered to be mutagenic or genotoxic. In a one-generation developmental toxicity study, the chemical was administered via oral gavage at dose levels of 0, 30, 100 or 300 mg/kg bw/day. Treatment-related systemic effects observed in parental animals at the 300 mg/kg bw/day dose group included reduced body weight, reduced food consumption, changes in organ weights and related histopathological changes. No adverse effects on reproductive parameters were observed in parental animals up to the 300 mg/kg bw/day dose group (including oestrous cycle, fertility index, gestation index and implantation rate). The number of stillborn pups was statistically increased in animals from the 100 and 300 mg/kg bw/day dose groups, but the number of delivered pups per group showed no statistically significant differences compared with controls. In the F1 generation pups from the 300 mg/kg bw/day group, the number of liveborn pups was statistically significantly lower and outside the historical control range. In the 300 mg/kg bw/day group, a statistically significantly increase in pup mortality was also observed within the first 4 days following birth, significantly reducing the viability index. A reduction of mean

body weight and body weight gain was also observed in pups from this dose group. The study provides evidence of adverse effects on parental animals and pup viability. The NOAEL for maternal toxicity and developmental were determined to be 100 mg/kg bw/day, and the NOAEL for reproductive toxicity was determined to be 300 mg/kg bw/day.

Health hazard classification

The 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 does not consider classification of physical hazards and environmental hazards. This is the current classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Health Hazards	Hazard Category	Hazard Statement
Reproductive and Developmental Toxicity	Catategory 1B	H360D: May damage the unborn child.

Summary of health risk

Public

No specific use patterns were identified in Australia.

No cosmetic or domestic uses were identified in Australia. Based on its international use patterns, there are no identified risks to the public that require management. However, if information becomes available indicating the chemical dose have consumer used, further risk management may be required.

Workers

Workers may come into contact with the chemical in various types of curable products, such as paints, coating, surface agent, and photosensitive substances. During product formulation, 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 handling incompletely cured 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, ocular and inhalation exposure are implemented (see Recommendation section).

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.

Conclusions

The conclusions of this evaluation are based on the information described in the statement. Obligations to report additional information about hazards under Section 100 of the Industrial Chemicals Act 2019 apply.

The Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks provided all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Recommendations

Workers

Advice to industry

The information in this report should be used by persons conducting a business or undertaking at the workplace (such as an employer) to determine the appropriate controls.

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

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker
- 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.

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:

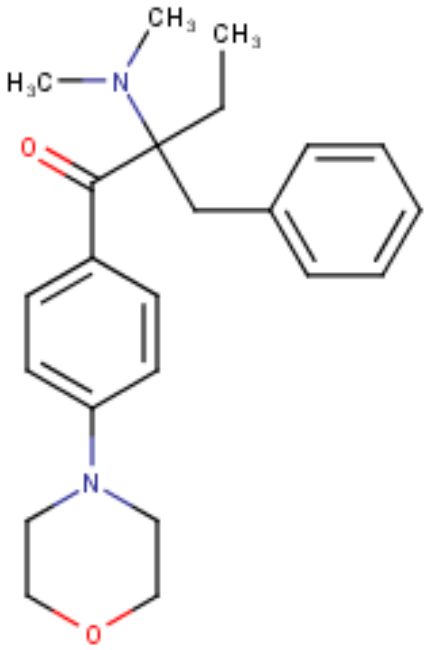
- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

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. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

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.

Supporting Information

Chemical identity

Synonyms	2-benzyl-2-dimethylamino-4-morpholinobutyrophenone benzyl dimethylamino morpholinophenyl butanone (INCI) Irgacure 369 UV 369
Structural Formula	
Molecular Formula	$C_{23}H_{30}N_2O_2$
Molecular Weight (g/mol)	366.50
SMILES	O=C(C1=CC=C(C=C1)N2CCOCC2)C(N(C)C)(CC=3C=CC=CC3)CC
Chemical Description	-

Relevant physical and chemical properties

Physical Form	Slightly yellow solid powder
Melting Point	113.2 °C
Boiling Point	Decomposes at >275 °C

Vapour Pressure	≤6 × 10^{-7} Pa at 25 °C
Water Solubility	5.9 mg/L at 20 °C
log K_{ow}	2.91

Introduction and use

Australia

No information is available on the use of this chemical in Australia.

International

The chemical has reported cosmetic use as a binding agent (CosIng).

The chemical has reported potential domestic uses, including as a:

- paint additive;
- surface coating additive;
- surface active agent.

Overall information indicates that domestic use is not likely to be widely available for domestic use. The REACH dossiers and Canadian reporting information (Government of Canada) did not identify any consumer uses of the chemical. Consumer use in inks toner and colourants were identified by only one company is in USA (US EPA, 2016). Consumer uses were identified in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that are produced from chemical reactions involving the chemical. There is no evidence from available consumer product databases for use of this chemical in consumer industrial products,

The chemical has reported commercial uses, including:

- as a process regulator;
- in photosensitive substances such as photo-initiators.

The chemical has site-limited industrial uses, including in the production of polymers. The chemical is used as photoinitiator in polymer production. The chemical generates free radicals using the energy of UV-light for the formation of polymeric materials. The main applications of the substance are in high speed inks such as flexo, offset litho and UV ink jet (ECHA, 2019)

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Reproductive and developmental toxicity – Category 1B; H360D (May damage the unborn child)

No exposure standards are available for this chemical in Australia (Safe Work Australia)

International regulatory status

Exposure standards

The following exposure standards are identified (Galleria Chemica):

- An occupational exposure limit (OEL) of 1 mg/m^3 for type 2 dust and 2 mg/m^3 for type 3 dust has been identified in Japan (Japan SOH, 2018).

European Union

The chemical is listed on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2020). The reason for inclusion is 'Endocrine disrupting properties (Toxic for reproduction (Article 57c)'. 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.

Health hazard information

Toxicokinetics

No specific toxicokinetic data are available for the chemical.

The available information on the chemical show that it is likely to be absorbed by the oral routes, based on the molecular weight (366.5 g/mol), moderate water solubility (5.9 mg/L at 20°C) and partition coefficient (log Pow = 2.91). Dermal absorption is slight to moderate as calculated by a skin penetration model (Fitzpatrick 2004), which mathematically calculates dermal penetration based on partition and diffusion equations of comparable solutions. Absorption via the respiratory tract is expected to be dependent on the particle size. It is expected that absorption via the dermal and inhalation routes would be lower than via the oral route.

Acute toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity. An LD50 of >5000 mg/kg bw was reported in Sprague Dawley rats (n = 5/sex/dose) administered the chemical at 2000 or 5000 mg/kg bw, based on a study conducted according to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 401 (REACH).

Dermal

Based on the available data, the chemical has low acute oral toxicity. A dermal LD50 of >2000 mg/kg bw was observed in Sprague Dawley rats (n = 5/sex/dose) administered with the chemical at 2000 mg/kg bw, based on a study conducted according to OECD TG 402 (REACH).

Inhalation

No data are available to evaluate this endpoint.

Corrosion/irritation

Skin irritation

Based on the available data from animal studies, the chemical is not irritating to the skin. In an in vivo skin irritation study, conducted in accordance with OECD TG 404, the chemical was applied to the skin of New Zealand White (NZW) rabbits (n = 3). No signs of skin irritation were observed for the full duration of the study (REACH).

Eye irritation

Based on the available data from animal studies, the chemical is considered to be slightly irritating to the eyes. In an in vivo eye irritation study conducted in accordance with OECD TG 405, the chemical was applied undiluted to the eyes of NZW rabbits (n = 3). The chemical produced low grades of corneal opacity, iritis, redness of the conjunctivae and chemosis within 1 hour after application. All effects were reversible within 24 to 48 hours (REACH).

Sensitisation

Skin sensitisation

The chemical was found to be non-sensitising in an in vivo skin sensitisation study conducted according to OECD TG 406 (guinea pig maximisation test (GPMT)). For induction, Pirbright-Hartley guinea pigs (n = 20) were induced intradermally with the chemical at 30% in saline. Topical induction used the chemical at 30% in petroleum jelly. After 2 weeks, the animals were topically challenged with the chemical at 10% in petroleum jelly. No skin reactions were observed in any of the control or treated animals. Therefore, the chemical was not considered to be a skin sensitiser on the basis of this study (REACH).

Repeat dose toxicity

Oral

In a repeated dose toxicity study conducted according to OECD TG 407, groups of Wistar rats (n = 5/sex/dose) were administered the chemical by gavage at doses of 0, 100, or 500 mg/kg bw/day for 28 days. At the highest doses of 500 mg/kg bw/day, severe effects were observed, such as hunched posture, piloerection, lean appearance, salivation, retching and/or gasping, and treatment was stopped after 9 days. After a 5 day recovery period, the same animals were treated at a reduced dose level of 250 mg/kg bw/day. Body weight loss (up to 14% of starting weight) or reduced weight gain was noted among all animals at 500 mg/kg bw/day. Upon re-commencement at 250 mg/kg/day, the body weights of females were similar to the control animals, but body weights of males were still slightly lower than control animals (achieving statistical significance). Body weight gain of animals in this group was similar to that observed in control animals after re-commencement. At 100 and 250 mg/kg bw/day, there were increased relative/absolute liver weights in males and a lower absolute spleen weight for females at 250 mg/kg bw/day, and lower relative spleen weight for females at 100 and 250 mg/kg bw/day. In the liver, hepatocyte hypertrophy was observed in 4/5 males and 5/5 females at 250 mg/kg bw/day. Increased incidence and severity of cortical hyaline droplets were observed in the kidneys of most males at 250 mg/kg bw/day. This was accompanied by a slightly increased incidence and severity of corticomedullary tubular basophilia. Hyaline droplets were observed in some males from lower dose groups with a reduced degree of severity. Greenish discolouration of the kidneys was observed in all animals at 250 mg/kg bw/day, and redish-brown discolouration of the liver was observed among most females at 250 mg/kg bw/day. There were no adverse effects detected in sperm motility. Based on these effects, an NOAEL of 100 mg/kg bw/day was determined in this study, though the toxic effects observed at 250 mg/kg bw/day may be residual effects from receiving doses of 500 mg/kg bw/day previously.

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

In vitro

The chemical was negative in an Ames bacterial reverse mutation assay in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 at concentrations up to 5000 µg/plate both with and without metabolic activation (REACH).

In a mammalian chromosome aberration test conducted in Chinese hamster ovary (CHO) cells according to OECD TG 473, the chemical was negative when tested at concentrations up to 220 µg/mL. No relevant nor reproducible increase in the number of cells with specific chromosomal aberrations were observed in the test groups where compared with negative controls. Cytotoxic effects were reported at 55 µg/mL and higher, with and without metabolic activation following 3 hours of exposure, at 13.8 µg/mL and higher without metabolic activation following 14 and 48 hours of exposure, and at 27.5 µg/mL and higher without metabolic activation following 24 hours of exposure (REACH).

The chemical was negative in a mammalian cell gene mutation assay conducted on mouse lymphoma L5178Y cells according to OECD TG 476 at concentrations up to 160 µg/mL. No biologically relevant increases in mutation frequency were observed. Cytotoxic effects were observed at 30 and 40 µg/ml without and 160 µg/ml with metabolic activation and at 80 µg/ml and above, without metabolic activation (REACH).

In vivo

The chemical was negative in a mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474. Chinese hamsters (8 animals/sex/time point) were administered a single dose of the chemical at 5000 mg/kg bw by oral gavage and euthanised at either 16, 24 or 48 hours post-treatment. Bone marrow tissue was harvested from animals and examined for incidence of micronucleated polychromatic erythrocytes (PCE). There were no PCE observed at any time point under the conditions of this study (REACH).

Reproductive and development toxicity

The chemical is classified for developmental toxicity. The available data support the current classification.

In a one-generation reproductive toxicity study conducted according to OECD TG 415, Wistar rats (20/sex/dose) were administered the chemical via oral gavage at 0, 30, 100 or 300 mg/kg bw/day during pre-mating (for a maximum of 74 days), mating, gestation and lactation periods. Observed treatment-related effects in F0 animals of both sexes in the mid and high dose groups included a significant reduction in body weight, reduced food consumption, and changed organ weights with associated histopathological changes. Minimal to slight mucosal hyperaemia was seen in the glandular stomach in most males of the high dose test group. Minimal mucosal hyperaemia was observed in males and females from the mid dose group and females from the high dose group. A dose-dependent weight increase was observed in the livers of mid and high dose animals which was correlated with minimal to slight hypertrophy of central to midzonal hepatocytes. Although no histopathological signs of hepatotoxicity were seen in animals from the high dose group, based on the magnitude of the relative liver weight deviations and the lack of hepatic clinical chemical data, the effects were regarded as adverse, whereas the effects in the mid dose group were regarded as adaptive. Green-brown or dark brown discolouration in the liver was noted upon necropsy and was consistent with brown-gold pigment storage in central hepatocytes at 300 mg/kg bw/day. This finding was minimal and was considered to be treatment-related but not adverse. No adverse effects were observed in treated animals in relation to reproductive parameters, including oestrous cycle, fertility index, gestation index and implantation rate. No abnormalities were observed in reproductive organs of any treated animals.

In the F1 generation, the number of liveborn pups was statistically significantly lower in the 100 mg/kg bw/day dose group (about 5% below control) and 300 mg/kg bw/day dose group (about 21% below control). The results for the 100 mg/kg bw/day dose group were within the historical control range, but the results for the 300 mg/kg bw/day dose group were outside the historical control range. In the high dose group, a statistically significantly increase in pup mortalities was observed within the first 4 days after birth, leading to a significantly reduction in the viability index. In all surviving pups in the high dose group, a reduction in mean body weight and body weight gain was observed and these were attributed to the reduced food consumption and body weight gain of lactating mothers from this dose group. The study provides evidence that the chemical can cause specific adverse effects on pup viability. The NOAEL for maternal toxicity and developmental toxicity was determined to be 100 mg/kg bw/day and the NOAEL for reproductive toxicity was determined to be 100 mg/kg bw/day. The

available data support the existing GHS classification for reproductive and developmental toxicity.

References

ECHA (European Chemicals Agency) (2019) proposal for identification of a substance of very high concern on the basis of the criteria set out in reach article 57. Substance Name: 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one. Accessed May 2021 at https://echa.europa.eu

ECHA (European Chemicals Agency) (2020) Inclusion of substances of very high concern in the Candidate List for eventual inclusion in Annex XIV. Accessed May 2021 at https://echa.europa.eu/documents/10162/ba42270a-93fe-7cde-6d41-7f7af4e00e66

European Cosmetic Ingredient Database (CosIng). Accessed May 2021 at https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.simple

Fitzpatrick D. Corish J. and Hayes B (2004) 'Modelling skin permeability in risk assessment - the future.' *Chemosphere* 55 (10): 1309–1314

Galleria Chemica. Accessed May 2021 at https://jr.chemwatch.net/galleria/

Government of Canada. Inventory updates conducted under Canada's Chemicals Management Plan (CMP). Government of Canada. Available at: https://www.canada.ca/en/health-canada/services/chemical-substances/inventory-updates.html

Japanese Society for Occupational Health (2018), 'Recommendation of Occupational Exposure Limits (2018-2019)', *Journal of Occupational Health* 60(5): 419-512.

Registration, Evaluation and Authorisation of Chemicals (REACH) Dossier. 2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone (CAS No. 119313-12-1). Available at: https://echa.europa.eu/information-on-chemicals/registered-substances

Safe Work Australia (SWA). Hazardous Chemicals Information System (HCIS). Accessed May 2021 at http://hcis.safeworkaustralia.gov.au/

UNECE (2017). Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Seventh Revised Edition. United Nations Economic Commission for Europe (UNECE), Geneva, Switzerland. Accessed May 2021 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev07/07files_e0.html

US EPA 2016. United States Environment Protection Agency Chemical Data Reporting (CDR) 2016 data, Accessed May 2021 at https://www.epa.gov/chemical-data-reporting/access-cdr-data