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

Retinoic acid, 3,3-dimethyl-2-oxobutyl ester

Assessment statement (CA09781)

15 April 2024

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AICIS assessment statement (CA09781)

Chemical in this assessment

Name	CAS registry number
Retinoic acid, 3,3-dimethyl-2-oxobutyl ester	893412-73-2

Reason for the assessment

An application for an assessment certificate under section 31 of the *Industrial Chemicals Act 2019* (the Act).

Certificate Application type

AICIS received the application in a Health Focus type.

Defined scope of assessment

The chemical has been assessed:

- as imported into Australia at up to 0.1 tonne/year
- as imported in formulations at up to 10% concentration for reformulation of end use cosmetic skincare products; and
- as imported or reformulated in leave-on skincare products (such as lotions, creams, and serums) at up to 0.5% concentration

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia. It will be imported either in formulations at up to 10% concentration for reformulation, or in end use leave-on skincare products such as lotions, creams and serums. The imported or reformulated end use products will contain the assessed chemical at up to 0.5% concentration and are proposed to be used by professional workers and by members of the general public.

Human health

Summary of health hazards

The submitted toxicological studies were conducted on the assessed chemical in neat form for acute oral toxicity and genotoxicity, and on the assessed chemical at low concentrations for the other endpoints listed below. Some of these are non-guideline studies or studies conducted with a limited number of human volunteers (see **Supporting information** section).

Based on the limited data provided, the assessed chemical is:

- of low acute oral toxicity
- of low acute dermal toxicity at up to 0.3% concentration
- not irritating to skin at up to 0.5% concentration
- not irritating to eyes at up to 0.1% concentration
- not expected to be a skin sensitiser at up to 0.5% concentration
- not expected to have systemic effects following repeated exposure to skin at up to 2% concentration, but may cause irritation effects at high doses
- not expected to be genotoxic
- not phototoxic at up to 0.1% concentration

In addition, the assessed chemical was predicted to be non-irritating to skin or eyes and non-sensitising to skin using a knowledge-based expert system for the qualitative prediction of toxicity (DEREK).

Hazard classifications relevant to worker health and safety

Based on limited data provided by the applicant, the assessed chemical cannot be classified according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety as adopted for industrial chemicals in Australia.

Summary of health risk

Public

There will be widespread and repeated exposure of the public to the assessed chemical at up to 0.5% concentration through the use of leave-on skincare products containing the assessed chemical (such as lotions, creams and serums). The principal route of exposure will be dermal, while incidental ocular exposure is also possible. Inhalation exposure is not expected given the estimated low vapour pressure of the assessed chemical and non-spray use of the skincare products.

Based on the quantitative risk assessment (QRA) for the worst-case scenario, consumers using leave-on skincare products (primarily for facial use) could be systemically exposed to the assessed chemical at approximately 128 µg/kg bw/day through repeated or prolonged exposure (see **Supporting information** section). This low exposure level is unlikely to pose health risk to the public with repeated use of products containing the assessed chemical. Furthermore, given this value is calculated using a dermal absorption (DA) rate of 100% as the worst-case scenario, the actual DA is expected to be low (see **Supporting information - Toxicokinetics** section), and therefore the actual systemic exposure is expected to be lower.

Overall, this assessment does not identify any risks to public health that would require specific risk management measures.

Workers

Reformulation workers may be incidentally exposed to the assessed chemical at up to 10% concentration during reformulation processes mainly via the dermal route, while ocular and inhalation exposures are also possible. To mitigate the risks to formulation workers from any repeated exposure, control measures would be required (see **Means for managing risk**) to minimise the exposure. It is anticipated by the applicant that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible. Use of appropriate personal protective equipment (PPE) such as safety glasses, impervious

chemical resistant gloves, protective clothing and respiratory protection will reduce worker exposure.

Professional workers in cosmetic businesses may experience exposure via dermal and accidental ocular exposure to the assessed chemical during the use of cosmetic products containing the assessed chemical at up to 0.5% concentration. The professional workers may wear some PPE such as gloves. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the same end use products containing the assessed chemical, requiring no specific risk management measures for these workers.

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data, the assessed chemical is:

- Not persistent (not P)
- Not Bioaccumulative (B)
- Not toxic (not T)

Environmental hazard classification

No aquatic toxicity information was available for the assessed chemical. Therefore, the assessed chemical is not able to be formally classified under the GHS (UNECE 2017) for acute and chronic aquatic toxicities.

Summary of environmental risk

The assessed chemical is a cosmetic ingredient to be included in skincare products. Use of these products is expected to result in the release of the assessed chemical “down the drain” and into the sewers. Consequently, the assessed chemical will be treated at sewage treatment plants (STPs) before release to surface waters.

The assessed chemical is not persistent, not bioaccumulative and not toxic. Hence the assessed chemical is unlikely to have unpredictable long-term effects. No ecotoxicity data were provided for the assessed chemical and risk quotients were not calculated. However, the assessed chemical will not be released to the environment in quantities that would pose a risk to aquatic life. The assessed chemical is rapidly biodegradable and expected to partition to particulate matters and sediments. On the basis of low introduction volume, lack of persistence and assumed low toxicity, the assessed chemical is not expected to pose significant risk to the aquatic environment. As such, the risk from the assessed chemical can be managed.

Means for managing risk

Workers

Information relating to safe introduction and use

The information in this statement 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.

The following control measures could be implemented to manage the risk arising from exposure to the assessed chemical during reformulation:

- Use of engineering controls such as
  - Enclosed and automated systems where possible
  - Adequate workplace ventilation to avoid accumulation of mists or aerosols

- Use of safe work practices to
  - Avoid contact with skin and eyes
  - Avoid inhalation of mists or aerosols

- Workers should wear the following personal protective equipment (PPE)
  - Impervious gloves
  - Protective clothing
  - Safety glasses
  - Respiratory protection where local ventilation may be inadequate

Conclusions

The Executive Director is satisfied that the risks to human health or the environment associated with the introduction and use of the industrial chemical can be managed.

Note:

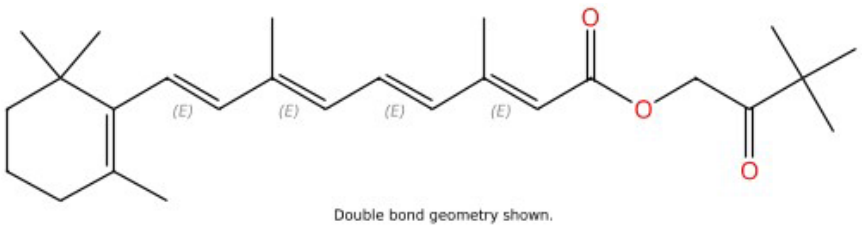
1. Obligations to report additional information about hazards under s 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	Retinoic acid, 3,3-dimethyl-2-oxobutyl ester
CAS No.	893412-73-2
Synonyms	3,3-Dimethyl-2-oxobutyl retinoate
Molecular formula	$C_{26}H_{38}O_3$
Molecular weight (g/mol)	398.6
SMILES (isomeric)	C(=C/C(=C/C=C/C(=C/C(OCC(C(C)(C)C)=O)=O)/C)/C)\C=1C(C)(C)CCCC1C

Structural formula



Double bond geometry shown.

Chemical description

The assessed chemical is the *all-(E)*-isomer with a purity of greater than 99.9%.

Relevant physical and chemical properties

Physical form	Yellow solid (crystalline)
Melting point	86 – 89 °C
Density	984 – 996 kg/m^3 at 15 °C
Particle size	> 1 mm
Vapour pressure	2.38 × 10^{-6} Pa at 25 °C (US EPA, 2012)
Water solubility	7.33 x 10^{-8} g/L (WSKOW v1.42, US EPA, 2012)
Ionisable in the environment?	No
log K_{ow}	8.93 (KOWWIN v1.68, US EPA, 2012)
log K_{oc}	5.12 (KOCWIN v2.00, US EPA, 2012)

Note: The assessed chemical is expected to decompose before boiling. However, no decomposition temperatures was provided.

Human exposure

Public

Dermal exposure

Skincare products (lotions, creams and serums) containing the assessed chemical will be primarily for facial use. Data on typical use of face creams (SCCS 2023) are shown in the following table. A dermal absorption (DA) rate of 100% was used as a worst-case scenario along with a combined average body weight (BW) for males and females of 60 kg for calculation purposes.

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (µg/kg bw/day)
Face cream	1,540	0.5	1	128

C = maximum intended concentration of assessed chemical; RF = retention factor
Daily systemic exposure = (Amount × C × RF × DA)/BW

Health hazard information

Toxicokinetics

The assessed chemical is an ester of all-*trans* retinoic acid (ATRA, also known as tretinoin). Based on its ester structure, it is expected to undergo enzymatic hydrolysis when absorbed into the body to produce tretinoin. However, its tert-butyl end group is expected to significantly reduce or inhibit such hydrolysis.

In an *in vitro* skin diffusion study, ^{3}H-isotopes of the assessed chemical (at 0.1% concentration) was applied onto human skin in an *in vitro* flow-through percutaneous cell system. The assessed chemical in the skin surface, stratum corneum, epidermis, dermis and receptor fluid were measured after 24 hours. Most of the assessed chemical was not absorbed, with ~96.79% remained on the skin surface. Of the assessed chemical that had penetrated through, ~0.99% and ~1.89% were recovered from the epidermis and stratum corneum respectively, and ~0.15% was recovered from the receptor fluid.

In an *in vivo* skin diffusion study, ^{3}H-isotopes of the assessed chemical (at 0.3% concentration) was applied onto human volunteers (n = 8), divided into two groups with one never exposed to the assessed chemical and the other group having 6 days of previous exposure to the assessed chemical (at 0.3% concentration). Of the administered dose, 2.5 – 5% were estimated to be absorbed into the skin. Less than 0.1% of the administered dose were found in excreta and no measurable radioisotopes were observed in plasma.

In a study designed to test for hydrolysis of the assessed chemical in the skin, the assessed chemical (at 0.3% concentration) was applied onto the skin of a human volunteer with adhesive tape. After the required exposure time, the tape was removed with part of the stratum corneum. The first tape was discarded as it contained unabsorbed test substance on the skin. Then the process was repeated over 4 tapes with 4 pulls each, and the combined contents of 16 tapes were exposed to ethyl acetate, filtered and its contents analysed by HPLC. No retinoic acid

was found in the collected contents, indicating enzymatic hydrolysis of the assessed chemical did not occur. Parallel studies conducted using a positive control was able to retrieve retinoic acid absorbed by the skin, confirming the validity of this study.

Based on the information provided, the assessed chemical is not easily absorbed through the dermal route. It is not expected to undergo hydrolysis to tretinoin and is instead expected to be metabolised by oxidation. However, its exact degradation pathway and metabolites in the human body are unknown.

Acute toxicity

Oral

In an acute oral toxicity study (similar to OECD TG 423), the assessed chemical was administered to Sprague-Dawley rats (n = 3/sex) at a single dose of 2,000 mg/kg bw via oral gavage. All animals survived during the 7-day observation period. No signs of systemic toxicity were noted. All animals showed expected body weight gains and no treatment-related gross necropsy findings were observed. The acute oral median lethal dose (LD50) of the test substance was determined to be > 2,000 mg/kg bw.

Corrosion/Irritation

Skin irritation

In an *in vitro* skin irritation study (similar to OECD TG 439 – Reconstructed Human Epidermis model) conducted on the assessed chemical at 0.5% concentration, the relative mean viability of the test substance-treated tissues was 92% after the 1-hour exposure period (followed by 43-hour post-incubation). As the tissue viability was > 50%, the test substance is considered as non-irritating to the skin.

A modified 21-day cumulation skin irritation test (non-guideline study) was conducted in human volunteers (n = 27) at 0.1% concentration of the assessed chemical. A 20 µL of the test substance was applied to the patch site of each test subject under occlusive conditions, for 24 hours each day for 12 consecutive days. Each day, new patches were applied after the site had been evaluated for irritation. Approximately 14 days after the final induction, a challenge patch was applied, and the challenge site was evaluated after 48 and 96 hours. The corrected cumulative irritation score was 0 and no allergic contact dermatitis was observed. Based on the results, the test substance is considered as non-irritant or non-sensitiser to the skin.

The assessed chemical was predicted to be non-irritating to skin using a knowledge-based expert system for the qualitative prediction of toxicity (DEREK).

Furthermore, the assessed chemical is also known as hydroxypinacolone retinoate (HPR). It is reported that HPR is non-corrosive and there is little to no skin irritation associated with dermal use of HPR (TGA 2022).

Eye irritation

In an *in vitro* eye irritation study (OECD TG 492 - EpiOcular™ model) conducted on the assessed chemical at 0.1% concentration, the relative mean viability of the test substance-treated tissues was 100% after 4 hours of exposure. As the tissue viability was > 60%, the test substance is considered as non-irritating to the eyes.

The assessed chemical was predicted to be non-irritating to eyes using a knowledge-based expert system for the qualitative prediction of toxicity (DEREK).

Sensitisation

Skin sensitisation

In a Human Repeat Insult Patch Test (HRIPT) conducted using the assessed chemical at 0.5% concentration, 50 human volunteers were applied with an occlusive patch dispensed with 0.2 mL of the test substance. The patch was applied onto the back of the test subject for 9 days (every Monday, Wednesday and Friday for 3 consecutive weeks), with 24-hour exposure each day. Ten to 14 days after the final induction, a challenge patch was applied onto an untreated site using the same dose, and the challenge site was evaluated for sensitisation after 24 and 48 hours. No adverse skin reactions were observed. Based on the results, the test substance is not expected to be a skin sensitiser.

The assessed chemical at 0.1% concentration did not induce allergic contact dermatitis in the modified 21-day cumulation skin irritation test in human volunteers (see **Skin irritation** section).

The assessed chemical was predicted to be non-sensitising to skin using a knowledge-based expert system for the qualitative prediction of toxicity (DEREK).

Repeat dose toxicity

Dermal

In a 14-day repeated dermal toxicity study (non-guideline study), 50 µL of each of 4 cream formulations (containing 0.1% or 0.3% assessed chemical) were topically applied to male Rhino mice (5 mice/group) for 14 consecutive days under semi-occlusive conditions. No signs of systemic toxicity were observed. One animal treated at 0.3% concentration died on day 12 and the study authors reported it as not treatment-related. Statistically but not biologically significant weight loss in treated animals was noted on day 7 but recovered on day 15. Local skin reactions included well defined erythema in 1 animal treated at 0.3% concentration, slight oedema in 2 animals treated at 0.3% concentration, and moderate scaliness in 4/20 treated animals, substantiated by histopathological findings of the epidermal surface of the skin (slight to moderate inflammatory activity and epithelial hyperplasia).

In a 90-day repeated dose dermal toxicity study (similar to OECD TG 411), the assessed chemical at 2% concentration was administered topically to rabbits (n = 4/sex/group) at 0, 6.26, 12.5 and 25 mg/kg bw/day for 88 days, under occlusive conditions. Due to signs of progressively worsening irritation, from day 59 the dosage was decreased to 2.44, 5.03 and 7.43 mg/kg bw/day for 1 week, then paused for 2 weeks. After irritation had moderated, the treatment continued at the lowered doses but was stopped on day 88 due to recurred irritation. There were no unscheduled deaths and no signs of systemic toxicity were observed. No treatment-related findings in the organs were observed at gross necropsy. Histopathological examination revealed secondary effects of the severe inflammatory skin lesions including increased incidence and severity of leukocytic emboli in the arterioles of the lung and myeloid hyperplasia in the bone marrow. Histological evaluation of the treated sections of the skin showed signs of irritation including dermal haemorrhage, mild to moderate acanthosis, hyperkeratosis and parakeratosis.

Genotoxicity

The assessed chemical was found to be non-mutagenic in a bacterial reverse mutation assay (OECD TG 471) using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. No biologically relevant increases in the frequency of revertant colonies were observed at up to 666.7 µg/plate, in the presence or absence of metabolic activation.

The assessed chemical was found to be non-clastogenic to Chinese Hamster Ovary (CHO) cells in an *in vitro* mammalian chromosome aberration test (OECD TG 473). The concentrations used in the main experiments (up to 143 µg/mL with and without metabolic activation) were based on data from a preliminary toxicity test. There were no biologically relevant increases in the frequency of chromosomal aberrations in cells treated at up to 143 µg/mL concentrations, in the presence or absence of metabolic activation.

Developmental toxicity

The assessed chemical, HPR, is a derivative of tretinoin which is classified as a Reproductive Toxicant Category 1 (H360 – May damage fertility or the unborn child) and included in Schedule 4 (prescription only medicines and prescription animal remedies) of the current Poisons Standard (SUSMP 2024). The Therapeutic Goods Administration (TGA) has made an amendment to exclude HPR in preparations for dermal use containing 0.5% or less from Schedule 4. As part of the reasoning, the decision has been made with consideration that developmental toxicity for the dermal exposure is unlikely to occur as conversion of HPR to tretinoin is unlikely (TGA 2022).

Phototoxicity

A cosmetic foundation containing 0.1% assessed chemical was found to be non-phototoxic when evaluated on 5 human subjects. The test substance was applied to the skin at a minimum concentration of 2 mg/cm^2 and the test site then received a UV-A light dosage of > 4.4 J/cm^2. The site was then covered with an occlusive patch containing additional test substance (0.2 mL or 0.2 g) for a period of 24 hours. The site was evaluated for effects immediately following the patch removal and at 24-hour, 48-hour, and 1-week time points. No adverse or unexpected effects were observed.

Environmental exposure

The assessed chemical will be imported into Australia either as a component in end use products or as a component of liquid formulations for reformulation into end use products. Significant releases of the assessed chemical to the environment are not expected during reformulation, transport or storage. Release of the products containing the assessed chemical to the environment due to accidental spills is expected to be absorbed on suitable materials, and disposed of in accordance with relevant Local, State, Territory and Federal regulations. Any unused product containing the assessed chemical is expected to be disposed of in accordance with relevant Local, State, Territory and Federal regulations.

The assessed chemical is a cosmetic ingredient to be included in skincare products. Use of these products will result in the release of the assessed chemical “down the drain” and into the sewers. Consequently, the assessed chemical will be treated at sewage treatment plants (STPs) before release to surface waters.

Environmental fate

Partitioning

The assessed chemical has a high predicted log Koc value (log Koc = 5.12). Therefore, the chemical is expected to partition to and become immobile in soils and sediments.

The assessed chemical is predicted to be very slightly water soluble (water solubility = 7.332 x 10^{-8} g/L). If the assessed chemical is released to surface water, it is expected to partition to particulate matters and sediments based on its very slightly water solubility and high log Koc value.

The assessed chemical is predicted to be very slightly volatile (vapour pressure = 2.38 x 10^{-9} kPa). During STP treatment, proportion of the assessed chemical partition to air is negligible based on SimpleTreat 3.0 model outputs (Struijs, 1996).

Degradation

Based on measured degradation in water of acceptable read across chemicals, the assessed chemical is categorised as not persistent.

The degradation and transformation of all-trans-retinoic acids (at-RA) in six different types of seawater (i.e. artificial seawater, unfiltered and filtered natural seawater, each with or without autoclave treatment) was examined in a laboratory experiment. Degradation and transformation products of at-RA were analysed using high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The results showed that at-RA could be rapidly degraded and transformed into other isomers such as 9-cis-RA and 13-cis-RA when entering seawater, both of these isomers were also degraded at the end of the experiment. Over 80% of at-RA was degraded in the first 48 hours regardless of the type of seawater. The presence of microorganisms and suspended organic matters could jointly facilitate the degradation and removal of at-RA from the water column. Half-life of at-RA was 1.9 - 8.5 hours and half-life of 9-cis-RA and 13-cis-RA was 2.4 – 19.8 hours in various seawater types (Yeung et al., 2022).

Bioaccumulation

The assessed chemical is potentially bioaccumulative based on its predicted log Kow value, however based on structural considerations the assessed chemical is categorised as not bioaccumulative.

No reliable bioaccumulation information was provided for the assessed chemical. The predicted partition coefficient of the assessed chemical is log Kow = 8.93, which exceeds the domestic bioaccumulation threshold of log Kow = 4.2 (EPHC, 2009). Therefore, the assessed chemical is potentially bioaccumulative. However, it is expected based on the chemical structure, that the ester moiety will be subjected to hydrolysis to release retinoic acid which is a naturally occurring substance which is metabolised by most organisms. Therefore, the chemical is not considered bioaccumulative.

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming 100% of the introduction volume is released into sewage treatment plants (STP) over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in STP

processes is based on its physicochemical properties, modelled by SimpleTreat 3.0 (Struijs, 1996). Based on the biodegradability and partitioning of the assessed chemical, a moderate proportion (21%) of the assessed chemical will undergo biodegradation while a large proportion (72%) of the assessed chemical is expected to partition to sludge. Total removal during STP treatment was estimated to be 93%. Therefore, 7% of the total introduction volume was estimated to be released to the aquatic environment.

The calculation of the PEC (Struijs, 1996; EPHC, 2009) is detailed in the table below:

Total Annual Import Volume	100	kg/year
Proportion expected to be released to sewer	100 %	
Annual quantity of chemical released to sewer	100	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	0.27	kg/day
Water use	200	L/person/day
Population of Australia	25.423	Million
Removal within STP	93 %	Mitigation
Daily effluent production	5,085	ML/day
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River	0.003	µg/L
PEC - Ocean	0.0003	µg/L

Environmental effects

Effects on aquatic Life

Acute toxicity

No ecotoxicity data were provided for the assessed chemical. However, read-across information available to AICIS from assessments of a structurally similar analogue (AICIS, 2022) indicates that substance and the natural decay and/or breakdown of this substance is unlikely to cause harm in the environment.

Predicted no-effect concentration (PNEC)

No ecotoxicity data were provided for the assessed chemical. Therefore, the predicted no-effects concentration (PNEC) was not calculated. However, based on the low hazard of a structurally similar analogue, is it unlikely that the PNEC of the assessed chemical will exceed the PEC of 0.003 µg/L.

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below:

Persistence

Not Persistent (Not P). Based on measured degradation in water of acceptable read across chemicals, the assessed chemical is categorised as Not Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on structural considerations, the assessed chemical is categorised as Not Bioaccumulative.

Toxicity

Not Toxic (Not T). Based on available read-across information for an acceptable analogue substance, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

The assessed chemical is not PBT and is hence unlikely to have unpredictable long-term effects (EPHC 2009). No ecotoxicity data were provided for the assessed chemical. Therefore, the Risk Quotients (RQ = PEC ÷ PNEC) was not calculated. However, the assessed chemical is not expected to be released to the environment in quantities that would pose a significant risk to aquatic life. The assessed chemical is expected to be rapidly biodegradable and expected to partition to particulate matters and sediments. On the basis of low introduction volume, lack of persistence, bioaccumulation potential, and assumed low toxicity, the assessed chemical is not expected to pose significant risk to the aquatic environment. As such, the risk from the assessed chemical can be managed.

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