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

Acetic acid, 2-cyano-2-[3-[(3-methoxypropyl)amino]-2-cyclohexen-1-ylidene]-, 2-ethoxyethyl ester, (2Z)-

Assessment statement (CA09589)

22 May 2023

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AICIS assessment

Chemical(s) in this assessment

Name	CAS registry number
Acetic acid, 2-cyano-2-[3-[(3-methoxypropyl)amino]-2-cyclohexen-1-ylidene]-, 2-ethoxyethyl ester, (2*Z*)-	1419401-88-9

Reason for the assessment

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

Certificate Application Type

Health Focus

The assessed chemical is an ultraviolet (UV) filter, meeting the criteria for a specified class of introduction under subsection 7(4)(a) of the *Industrial Chemicals (General) Rules 2019* (the Rules).

Defined scope of assessment

The chemical has been assessed:

- as imported into Australia at up to 2 tonnes per year
- as a component of cosmetic (secondary sunscreen) products at a concentration up to 3%
- for use by consumers and professional workers
- as not used in combination with nitrosating substances and the nitrosamine content in products is less than 50 parts per billion

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia. It will be imported into Australia as a component of finished cosmetic sunscreen products at less than or equal to 3% concentration in sealed containers. These containers will be stored in warehouses prior to distribution to retail outlets by road. The cosmetic sunscreen products will be imported in tubes, bottles, pump bottles, pump sprays (non-aerosol) and sticks, in packaging sizes between 5 mL and 300 mL.

The cosmetic (secondary sunscreen) products containing the assessed chemical at a concentration of 3% or less will be widely used by consumers. However, there is also the potential for these products to be used by workers in beauty salons when applying these

products prior to the application of other cosmetics/personal care products, and by workers working outdoor for protection from sun exposure, as is the case for consumers.

The assessed chemical is a secondary amine which is prone to nitrosation and formation of nitrosamines. The applicant has stated that the assessed chemical will not be used in combination with nitrosating substances and the nitrosamine content in products will be less than 50 parts per billion as suggested by the European Commission Scientific Committee on Consumer Safety (SCCS) in the *Opinion on Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87) - Submission II* (SCCS 2019).

Human health

Summary of health hazards

The available data indicates that the assessed chemical:

- is of low acute oral toxicity
- is not irritating to skin and eyes
- is not a skin sensitiser
- is not a skin photoirritant or photosensitiser
- is not considered to be genotoxic
- is of low dermal absorption
- is not likely to cause systemic toxicity following repeated oral exposure up to 300 mg/kg bw/day
- is not likely to cause adverse effects on male and female reproductive organs, embryotoxicity or teratogenicity following repeated oral exposure up to 2500 mg/kg bw/day.

No inhalation toxicity data were provided for the assessed chemical.

Hazard classifications relevant for worker health and safety

The chemical does not satisfy the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017), as adopted for industrial chemicals in Australia.

Summary of health risk

Public

When introduced and used in the proposed manner, there will be widespread and repeated exposure of the public to the finished cosmetic sunscreen products containing the assessed chemical at a concentration of 3% or less. As the product will be manually applied to the face and/or body and potentially sprayed on the body (not the face) with a non-aerosol pump spray, the principal route of exposure will be dermal though ocular exposure is possible.

The repeated dose toxicity potential of the assessed chemical was estimated by calculating the margin of exposure (MoE), with total daily systemic exposure estimated as 0.1257 mg/kg bw/day (see Human exposure section under **Supporting information**). Using a No-observable-adverse-effect-level (NOAEL) of 300 mg/kg bw/day, which was derived from a repeated dose oral toxicity study on the assessed chemical, the MoE was estimated to be

2387. A MoE value of greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences, therefore, the MoE is considered to be acceptable.

This assessment does not identify any risks to public health that would require specific risk management measures when the assessed chemical is introduced in accordance with the terms of the assessment certificate.

Workers

The cosmetic sunscreen products containing the assessed chemical at a concentration of 3% or less will be widely used by consumers. However, there is also the potential for these products to be used in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. workers in beauty salons). In addition, products containing the assessed chemical at a concentration of 3% or less could be used by workers working outdoor for protection from sun exposure, as is the case for consumers.

This assessment does not identify any risks to the health of workers that would require specific risk management measures when the assessed chemical is introduced in accordance with the terms of the assessment certificate.

Environment

Summary of environmental hazard characteristics

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

- Persistent (P)
- Not bioaccumulative (not B)
- Not toxic (not T)

Environmental hazard classification

The chemical satisfies the criteria for classification according to the GHS (UNECE 2017) as Acute Category 3 (H402) and Chronic Category 3 (H412) based on the measured toxicity to aquatic plants. Considerations were also made for the assessed chemical being not rapidly degradable:

Environmental Hazard	Hazard Category	Hazard Statement
Acute Aquatic	Acute aq. – Cat. 3	H402: Harmful to aquatic life
Chronic Aquatic	Chronic aq. – Cat. 3	H412: Harmful to aquatic life with long lasting effects

Summary of environmental risk

The assessed chemical will be introduced as a UV filter for use in cosmetic sunscreen products. This use may result in the release of the assessed chemical to sewers and directly to surface waters during recreational activities. Following release to water, most of the assessed chemical is expected to stay in the water compartment while a small amount will adsorb to sediment.

The assessed chemical is not readily- or inherently degradable and is stable to hydrolysis. Thus, the assessed chemical is considered to be persistent. The assessed chemical is not bioaccumulative and is not toxic to aquatic organisms, according to domestic environmental hazard thresholds.

Although the assessed chemical is persistent, it does not meet all three PBT criteria. The environmental risk may be estimated by the risk quotient method (RQ = PEC ÷ PNEC). Based on calculated RQ values < 1 for the river and ocean compartments, it is expected that the environmental risk from the introduction of the assessed chemical can be managed.

Means for managing risk

No specific means for managing risk are required when the assessed chemical is introduced in accordance with the terms of the assessment certificate.

Conclusions

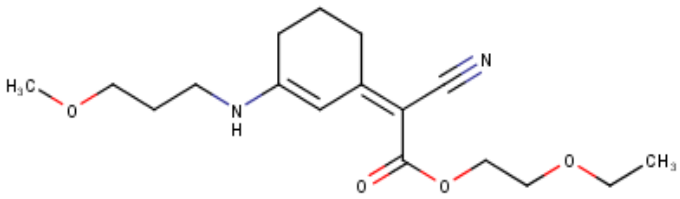
The conclusions of this assessment are based on the information described in this statement.

The Executive Director is satisfied that when the assessed chemical is introduced and used in accordance with the terms of the assessment certificate, the human health and environment risks can be managed. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Note: Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	Acetic acid, 2-cyano-2-[3-[(3-methoxypropyl)amino]-2-cyclohexen-1-ylidene]-, 2-ethoxyethyl ester, (2*Z*)-
CAS No.	1419401-88-9
Synonyms	2-Ethoxyethyl (2*Z*)-2-cyano-2-[3-[(3-methoxypropyl)amino]-2-cyclohexen-1-ylidene]acetate (IUPAC name) Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (INCI name) Uvinul® LR
Molecular formula	$C_{17}H_{26}N_2O_4$
Molecular weight (g/mol)	322.41
SMILES	N#CC(C(=O)OCCOCC)=C1C=C(NCCCOC)CCC1 (canonical) C(\C(OCCOCC)=O)(/C#N)=C/1\C=C(NCCCOC)CCC1 (isomeric)
Structural formula	

Relevant physical and chemical properties

Physical form	Yellow powder
Melting point	93.1 °C
Boiling point	306 – 315 °C
Vapour pressure	< 1.3 × 10^{-6} Pa at 20 °C
Water solubility	450 mg/L at 20 °C
Henry's law constant	8 × 10^{-9} Pa.m^3/mol
Ionisable in the environment?	Yes, the amine will be almost fully protonated at pH 4–9

pKa	13.3 at 20 °C
log Kow	1.7
log Koc	1.9

International regulatory status

European Union

This substance is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area, at less than 10 tonne per annum for use by consumers. This chemical is listed under Cosmetic Products Regulation, Annex VI - Allowed UV Filters.

In December 2019, the European Commission Scientific Committee on Consumer Safety (SCCS 2019) concluded that based on the data submitted, the use of Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate (S87, CAS 1419401-88-9) as a UV-filter in cosmetic products up to a maximum concentration of 3%, is safe. However, inhalation toxicity was not assessed as no data were provided, therefore, the SCCS Opinion is not applicable to any sprayable products that could lead to exposure of the consumer's lung by inhalation.

It was also stated that as S87 is a secondary amine, and thus is prone to nitrosation and formation of nitrosamines. It should not be used in combination with nitrosating substances. The nitrosamine content should be < 50 ppb.

Human exposure

Workers

Transport, storage and warehouse workers are not expected to be exposed to the assessed chemical, except in the unlikely event of an accidental rupture of containers.

Exposure to the assessed chemical in end use products at up to 3% concentration may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. workers in beauty salons). In addition, products containing the assessed chemical at a concentration of 3% or less could also used by workers working outdoor for protection from sun exposure, just as is the case for consumers. In these situations, the products will be manually applied to the face and/or body and potentially sprayed on the body (not the face) with a non-aerosol pump spray. The principal route of exposure will be dermal, though unintentional ocular exposure is also possible. Exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the cosmetic sunscreen products containing up to 3% of the assessed chemical.

Public

There will be widespread and repeated exposure of the public to the assessed chemical at a concentration of 3% or less through the use of cosmetic sunscreen products. Consumers will apply a small amount of product containing the assessed chemical at a concentration of 3% or less to sun-exposed skin areas. The product will be manually applied to the face and/or body and potentially sprayed on the body (not the face) with a non-aerosol pump spray.

Typically, 18 grams of sunscreen product will be applied per day. The principal route of exposure will be dermal though unintentional ocular exposure is also possible.

Data on typical use patterns of products (SCCS 2012) in which the sunscreen products containing the assessed chemical may be used are shown in the following table. For the purposes of the exposure assessment, Australian use patterns are assumed to be similar to those in Europe. A dermal absorption (DA) rate of 2.65% (SCCS 2019) and a lifetime average female body weight (BW) of 70 kg (enHealth 2012) were used for calculation purposes. A combined internal dose of 0.0654 mg/kg bw/day was estimated.

It is noted that the above assumptions are less conservative as compared to the volume of 18 g/day stated by the applicant. In this case, an exposure scenario of 18 g/day of sunscreen product applied per day would result in an internal dose of 0.1257 mg/kg bw/day (results not shown).

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	3	1	0.0546
Face cream	1540	3	1	0.0176
Total				**0.0654**

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

Health hazard information

Toxicokinetics

Dermal Absorption

A dermal absorption study was conducted on the assessed chemical using an in vitro static diffusion cell apparatus with human skin (4 donors) (OECD TG 428). A representative cosmetic sunscreen formulation containing the assessed chemical at 3% concentration was applied to human skin samples and percutaneous absorption was assessed by collecting receptor fluid from the receptor chamber at 0, 0.5, 1, 2, 4, 8 and 24 h post dose.

At 24 h post dose, the amount considered as absorbed was estimated to be at maximum 1.08 ± 0.67 µg/cm^2 corresponding to 1.63 ± 1.02% of the applied dose, indicating penetration through split-thickness human skin to a low extent.

Acute toxicity

Oral

No acute oral toxicity data are available for the assessed chemical and the applicant has submitted data from an analogue chemical.

In an acute oral toxicity study (OECD TG 423), an analogue chemical was orally administered to female SD rats (n = 3/dose) at 300 and 2000 mg/kg bw. While there were no mortalities, signs of hypoactivity and piloerection were observed in all animals at 2000 mg/kg up to 2 days after dosing. Staggering gait (2 animals) and runny nose (all animals) were also observed on

day 2 after dosing. The oral median lethal dose (LD50) was determined to be greater than 2000 mg/kg bw indicating that the assessed chemical is likely to be of low acute oral toxicology.

Corrosion/Irritation

Skin irritation

The assessed chemical was determined not to be irritating to the skin in two in vitro skin irritation tests using the three-dimensional reconstructed human epidermis tissue model (EpiDerm^{TM} tissue) (OECD TG 439). The mean viability of the test-substance treated tissues in two studies was determined to be 101% and 124% after 60 minutes exposure (followed by 42 hours post-exposure incubation). Under the conditions of these studies and according to the test guideline, the assessed chemical was not considered to be irritating to the skin.

Eye irritation

The assessed chemical was tested for eye irritation potential using the three-dimensional reconstructed human cornea model (EpiOcular™) (OECD TG 492). Tissues were incubated with the test material in 3 dosing patterns at 50 mg (corresponding to ca. 83.3 mg/cm^2), 50 µL (corresponding to ca. 8mg per tissue), and 50 µL of a 3% (w/w) suspension for 6 hours followed by an 18-hour post-incubation period. Tissue destruction was determined by a colorimetric test measuring mean cell viability, with a mean cell viability of less than 50% indicative of eye irritation potential. The relative mean viability of each dosing pattern was 93.6% (50 mg), 106.5% (50 µL) and 103.6% (50 µL), respectively. Based on the results and as per the test guideline, the test substance is considered non-irritating to the eyes.

The eye irritation potential of the assessed chemical was further assessed in the Bovine Corneal Opacity and Permeability (BCOP) test by application of 750 µL of a 20% (w/v) solution of test material onto the epithelial surface of isolated bovine cornea for 4 hours (OECD TG 437). An In vitro Irritancy Score (IVIS) was calculated, with an IVIS greater than 55 being indicative of risk of serious damage to eyes. The IVIS score of the test-substance was determined to be 5.4. Based on the results and as per the test guideline, the test substance does not cause serious eye damage in the BCOP test under the test conditions chosen.

Overall, based on the available information, the assessed chemical is not classified as an eye irritant.

Sensitisation

Skin sensitisation

In a local lymph node assay (LLNA) (OECD TG 429), the test substance was administered to both ears of female CBA/J mice (5 animals/group) at 10%, 25% and 50% concentration (25 µL/ear) for 3 consecutive days. No clinical signs of toxicity or changes in body weights were observed in response to the test substance. Stimulation indices of 1.1, 1.0, and 1.0 were obtained for 10%, 25% and 50% test substance concentrations, respectively.

Based on the results, the test substance was not considered a skin sensitiser under the experimental conditions of this study.

Photosensitisation

The skin photosensitising potential of the assessed chemical was evaluated in guinea pigs, based on the Non-Adjuvant Method of Unkovic et al. (1988) (non-guideline study, similar to OECD TG 406 [Guinea Pig Maximization Test for skin sensitisation]). GLP standards were as per the Ministry of Health, Labour and Welfare, Japan (1997) and the guidelines were as per the Ministry of Health and Welfare, Japan (1989). Male Slc:Hartley guinea pigs were induced once daily for 6 days and then challenged after 16 days (Day 22) with the test substance at 50% (w/v) concentration, both with (10 animals) and without (5 animals) UV-irradiation, along with a vehicle control (5 animals) and positive control groups with (5 animals) and without UV-irradiation (5 animals). Observation was for 24 and 48 hours with challenge scores determined based on skin reactions.

No erythema was observed at any challenge site with the test substance in any of the vehicle control or treated groups. The degree of erythema observed in the positive control groups demonstrated that this study was conducted under the appropriate conditions.

Based on the results, the assessed chemical was considered to have no skin photo-irritating or photosensitising potential when tested at up to 50% (w/v) in *N*,*N*-dimethylformamide.

Repeat dose toxicity

Oral

In a repeated dose oral toxicity study (OECD TG 408), the assessed chemical was administered to Crl:WI(Han) rats (10/sex/dose) by oral gavage for 90 days at 100, 300, and 1000 mg/kg bw/day.

Test substance-related adverse effects were not noted in male/female animals at 100 mg/kg bw/day. At 300 mg/kg bw/day, urine-stained abdominal fur and an increased incidence of dehydration were noted in males and females. These findings were not considered adverse. Even though increases in liver weights of less than 10% in males and more than 10% in females, compared to respective control means, were observed, there were no histopathological correlates or any evidence of impaired organ function by clinical chemistry parameters. Therefore, the liver weight changes at 300 mg/kg bw/day were considered as test substance-related but were not considered adverse. Administration of the test substance at dose levels as high as 300 mg/kg bw/day did not result in any microscopic lesions in the liver that could be attributed to the test substance.

At 1000 mg/kg bw/day, all male and female rats survived until scheduled euthanasia. Mean body weight gains, food consumption and ophthalmic changes were unaffected by the administration of the test substance. Urine-stained abdominal fur noted in males and females and the number of animals affected achieved statistical significance ($p \leq 0.01$) at 1000 mg/kg bw/day. Total bilirubin, triglyceride, and glucose were significantly reduced ($p \leq 0.05$) in male rats at 1000 mg/kg bw/day on Day 91. Total bilirubin, cholesterol, and phosphorus were also significantly increased ($p \leq 0.05$) in female rats at 1000 mg/kg bw/day on Day 91. There were statistically significant changes in other organ weights, but there were no patterns, trends or associated microscopic findings to identify them as being toxicologically relevant. Liver weights were increased more than 10% in males and females compared to the corresponding control means, with minimal centrilobular hepatocellular hypertrophy as a histopathological correlate noted in 5/10 males and 8/10 females.

Under the conditions of this study, the NOAEL was established at 300 mg/kg bw/day for male and female rats.

Genotoxicity

In vitro genotoxicity

The assessed chemical was found to be non-mutagenic in a bacterial reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA-, with or without metabolic activation (OECD TG 471).

The assessed chemical was tested for its clastogenic and aneugenic potential in an in vitro mammalian micronucleus test using human lymphocytes (OECD TG 487). Pronounced cytotoxicity was noted following 3-hour exposure without and with S9-mix at 1225 µg/mL and above and following 24-hour exposure without S9-mix at 95.23/158.7 µg/mL and above. The test substance induced micronuclei in cultured human peripheral lymphocytes when tested for 3 hours in the absence and presence of metabolic activation. In the same test system, the test substance did not induce micronuclei when tested up to toxic concentrations (up to 155 µg/mL) for 24 hours in the absence of S9-mix. Overall, the assessed chemical is unlikely to be clastogenic or aneugenic (see comment at the end of this section).

The genotoxic potential of the assessed chemical was further explored by assessing induction of micronuclei in the reconstructed skin micronucleus assay (RSMN) in the EpiDerm™ model (non-guideline study, based on OECD TG 487). The EpiDerm™ tissues were treated either 2 or 3 times, 24 hours apart, with tissues processed at 48 hours (2-day dosing regimen) or at 72 hours (3-day dosing regimen). The percentage of cells with micronucleated binucleated cells in the test substance-treated tissues was not significantly increased relative to the vehicle control at any concentration tested in either the 2-day or 3-day dosing regimen. Based on the findings of this study, the test substance was concluded to be negative for the induction of micronuclei in the reconstructed skin micronucleus assay (RSMN) in EpiDerm™.

The assessed chemical was also assessed for its potential to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in CHO cells in vitro (OECD TG 476). The results indicated that treatment with the test substance did not lead to a relevant increase in the number of mutant colonies either with or without S9-mix. Thus, under the experimental conditions of this study, the test substance is not mutagenic in the HPRT locus assay under in vitro conditions in CHO cells in the presence or absence of metabolic activation.

In vivo genotoxicity

The assessed chemical was evaluated for its genotoxic potential (clastogenicity/aneugenicity) as measured by its ability to increase the incidence of micronucleated polychromatic erythrocytes in bone marrow of male and female Sprague-Dawley (Hsd:SD, 5/sex/group) rats (OECD TG 474). The test substance was administered twice, 24 hours apart, by oral gavage at 500, 1000, and 2000 mg/kg/day. In all high dose group animals, piloerection was noted after the second administration of 2000 mg/kg (day 1) which persisted in the males until euthanasia (day 2). These adverse effects were considered to represent evidence of systemic exposure of treated animals to the test substance.

It is noted that the test substance induced micronuclei in cultured human peripheral lymphocytes when tested for 3 hours in the absence and presence of metabolic activation. The SCCS (SCCS 2019) noted that, as an alternative to the above test, the assessed chemical did not induce micronuclei in a reconstructed skin micronucleus assay (RSMN) in the EpiDerm™

model. This model, currently under validation, has already been demonstrated to be sensitive to the clastogenic/aneugenic activity of a variety of chemicals and is considered especially relevant for chemicals for which human exposure is expected to be dermal. Furthermore, the SCCS stated that the Epiderm™ model has been shown to be more permeable than human skin and the applied dose is higher in this test than expected in human.

The test substance also did not induce any statistically significant increases in the frequency of cells with micronuclei in polychromatic erythrocytes in bone marrow, indicating that the assessed chemical was neither clastogenic nor aneugenic. Taken together, it is concluded that the assessed chemical is unlikely to be clastogenic or aneugenic.

Reproductive and developmental toxicity

Reproductive and developmental toxicity

In a reproductive/developmental toxicity screening study (OECD TG 421), the assessed chemical was administered to Crl:WI(Han) rats (10/sex/group) via oral gavage at dose levels of 100, 250 and 700 mg/kg bw/day, once daily for 14 days prior to cohabitation, during cohabitation, and continuing through the day before euthanasia for male rats or through Day 4 of lactation for female rats that delivered a litter. Female rats that did not deliver a litter were euthanized on an estimated Day 25 of presumed gestation.

Urine-stained abdominal fur was observed at all dose levels and achieved statistical significance at 100 mg/kg bw/day and higher dose levels in parent (P generation) males and at 700 mg/kg bw/day during lactation in P generation females. Mating and fertility parameters in the male rats and oestrous cycling, mating, fertility parameters, gestation, and lactation in the female rats were unaffected by administration of the test substance at dose levels as high as 700 mg/kg bw/day. Reproductive organ weights were also not altered by the administration of the test substance.

Mean pup weights per litter on Days 1 and 5 of lactation were slightly reduced (9% reduction and 14% reduction relative to control group values, respectively) in the 700 mg/kg bw/day dose group. This reduction in foetal body weights probably related to maternal toxicity, as the reductions iv n pup weights were concurrent with decreased maternal body weight change (17% reduction, relative to the control group value) and also the slightly higher mean litter size (11.2 versus 10.4 in the control group). There were no adverse clinical signs or gross lesions in the F1 generation pups.

Based on these results, the NOAEL for parental (general) toxicity was considered to be 250 mg/kg bw/day, based on urine-stained abdominal fur in female rats reaching statistical significance at 700 mg/kg bw/day and also maternal body weight decrease of 17% at 700 mg/kg bw/day. The NOAEL for reproductive toxicity was also considered to be 250 mg/kg bw/day, based on the reductions in mean pup weights per litter at 700 mg/kg bw/day. Further, these reductions in mean pup weights per litter were not observed in the lower dose groups (100 and 250 mg/kg/day), where evidence of maternal toxicity was not apparent. The NOAEL for effects on fertility was found to be 700 mg/kg bw/day (the highest dose tested). Based on the study results, the test substance did not display adverse effects on reproduction parameters.

Prenatal Development

In a prenatal developmental toxicity study (OECD TG 414), the assessed chemical was administered to pregnant female Crl:WI(Han) rats (25 rats/group) by oral gavage at dose levels

of 100, 250 and 700 mg/kg bw/day, once daily on gestational days 6 through 20. No deaths were attributed to the administration of the test substance at any dose level. Urine-stained abdominal fur was observed at all dose levels, including the control group. However, the numbers of animals affected with this clinical sign was higher in the 250 mg/kg bw/day dose group and achieved statistical significance ($p \leq 0.01$) in the 700 mg/kg bw/day dose group. This clinical sign was attributed to administration of the test substance.

Mean maternal body weights and body weight gains (absolute and corrected for gravid uterine weights) were significantly reduced during the study period at 700 mg/kg bw/day. Likewise, mean absolute and relative food consumption values in this dose group were reduced by 14% and 12%, respectively. No other ovarian or uterine examination, or litter parameters were affected by administration of the assessed chemical. Foetal body weight averages were significantly reduced by 6-7% in the 700 mg/kg bw/day dose group.

Foetal examination revealed statistically significant ($p \leq 0.05$) decreases in ossification site averages, relative to the respective control group values, in the caudal vertebrae and hind limbs at a maternally toxic dose (700 mg/kg bw/day), with the exception of hindlimb tarsals. However, there were no test substance-related effects on the incidence of malformations (irreversible changes in development) or other variations (reversible delays or accelerations in development). The reductions in ossification site averages correlated with reductions in foetal body weights at 700 mg/kg bw/day. Reductions in foetal body weights frequently occur at a maternally toxic dose concurrent with reduced maternal food consumption and maternal body weights, as seen in the current study.

A NOAEL of 250 mg/kg bw/day was selected for maternal and embryo-foetal toxicity, based on reductions in foetal body weight averages and the mean number of reduced ossification sites in the caudal vertebrae and hind limbs, which occurred in the 700 mg/kg bw/day dose group and were probably related to maternal toxicity. The incidence of animals with urine-stained abdominal fur also achieved statistical significance ($p \leq 0.01$) in the 700 mg/kg bw/day dose group.

Environmental exposure

The assessed chemical will be imported into Australia fully finished as a component in cosmetic sunscreen products. Significant release of the assessed chemical is not expected during transport or storage.

The assessed chemical is a UV filter in cosmetic sunscreen products. This use of the assessed chemical is expected to result in the release of the assessed chemical either “down the drain” and into the sewers or directly into surface waters from the skin of recreational water users. As such, some of the assessed chemical will be processed at sewage treatment plants (STPs) before release to surface waters, while some of the chemical may be released and exposed directly to recreational water bodies.

Environmental fate

Dissolution, speciation and partitioning

The assessed chemical contains an ionisable secondary amine. The measured pKa is 13.3, so the assessed chemical is expected to be almost entirely in the cationic or protonated form in the environmental pH range (4–9). The assessed chemical is moderately soluble, with a measured water solubility of 450 mg/L at 20 °C. The measured vapour pressure ($< 1.3 \times 10^{-6}$ Pa at 20 °C) and calculated Henry’s Law constant (8×10^{-9} Pa.m^3/mol) both indicate that the

chemical is only very slightly volatile, including from water and moist or dry organic matter. Therefore, exposure or partitioning to the air compartment is expected to be minimal.

The measured log K_{OW} (1.7) and log K_{OC} (1.9) values indicate the assessed chemical has low lipophilicity, so a small amount of the chemical may partition to soils and sediments, where high mobility is expected.

Based on the moderate water solubility, very slight volatility and high mobility in soil and sediment, the majority of the assessed chemical is expected to remain in the water compartment, and exposure to the soil and sediment compartments is expected to be minimal.

Degradation

Based on its low measured biodegradation in aquatic systems and hydrolytic stability, the assessed chemical is considered to be persistent.

A biodegradation study in water indicates that the assessed chemical is not readily- or inherently biodegradable. Less than 10% degradation was observed over 28 days in the supplied biodegradation study (OECD TG 301B).

A study on hydrolysis conducted according to OECD TG 111 indicates that the assessed chemical is hydrolytically stable (< 10% hydrolysed within 5 days at pH 7 and 50 °C) with an extrapolated half-life at pH 7 and 20 °C exceeding 500 days. The same hydrolysis study reported half-lives of 25.3 days at pH 4 and 20 °C and 1204 days at pH 9 and 20 °C.

UV filters may be removed from the environment through phototransformation processes. However, no information is currently available for the assessed chemical.

Bioaccumulation

Based on its log K_{OW} value, the assessed chemical has low bioaccumulation potential and is not expected to be bioaccumulative.

No measured bioaccumulation studies were provided for the assessed chemical. The measured partition coefficient of the assessed chemical (log K_{OW} = 1.7, OECD TG 117) is below the domestic threshold of 4.2 for bioaccumulation in aquatic organisms. Bioaccumulation in terrestrial and marine food webs of air breathing organisms is also not expected because the chemical is not expected to partition to air and the log K_{OW} is less than 2 (EPHC 2009).

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 (STPs). This calculated value is conservative as not all uses of the assessed chemical are expected to result in release to STPs. Based on its very low vapour pressure, moderate water solubility, lack of degradation and moderate lipophilicity, only a small proportion of the chemical is expected to be removed during treatment. As a result, the majority of the assessed chemical is expected to remain in STP effluent. The extent to which the assessed substance is removed from the effluent in STP processes is based on its physicochemical properties, modelled by SimpleTreat 3.0 (Struijs 1996) and is estimated to be 1% through adsorption to biosolids. Therefore 99% of the total introduction volume is estimated to be released to the aquatic environment. The calculation of the PEC is detailed in the table below:

Total Annual Import Volume	2000	kg/year
Proportion expected to be released to sewer	100 %	
Annual quantity of chemical released to sewer	2000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	5.48	kg/day
Water use	200.0	L/person/day
Population of Australia	25.423	Million
Removal within STP	1 %	Mitigation
Daily effluent production	5 085	ML/day
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	1.07	µg/L
PEC - Ocean	0.107	µg/L

Release of UV filters used in cosmetic sunscreen products from the skin of recreational water users, particularly swimmers, is an additional environmental exposure pathway for the assessed chemical. While some UV filters have been detected in freshwater and in ocean monitoring, no information is available for the assessed chemical or structural analogues of the chemical.

Environmental effects

Effects on Aquatic Life

Acute toxicity

The following measured median lethal concentration (LC50) and measured and calculated median effective concentration (EC50) values for model organisms were supplied by the applicant:

Taxon	Endpoint	Method
Fish	96 h LC50 = 67.8 mg/L	*Danio rerio* (zebrafish) Mortality OECD TG 203 Static conditions Nominal concentration
Invertebrates	48 h EC50 > 100 mg/L	*Daphnia magna* (water flea) Immobility OECD TG 202 Static conditions Nominal concentration
Algae	96 h EC50 = 1.6 mg/L	Green algae *In silico* methodology ECOSAR v1.11 (vinyl/allyl nitriles ECOSAR class)
Aquatic plants	7 d EC50 = 10.7 mg/L	*Lemna gibba* (gibbous duckweed) Growth rate of dry weight OECD TG 221 Static conditions Nominal concentration
Aquatic microorganisms	3 h EC10 > 1000 mg/L	Activated sludge Respiration inhibition OECD TG 209 Static conditions Nominal concentration

The reported endpoint for algae is the lowest calculated value in the ECOSAR v1.11 *in silico* modelling supplied for the assessed chemical. This modelling uses calculated inputs for log K_{OW} and water solubility, which were higher and lower, respectively, than the measured values. The choice of the vinyl/allyl nitriles ECOSAR class is consistent with this functionality being present in the assessed chemical, noting that predicted endpoints were also available for the aliphatic amines and esters ECOSAR classes. This modelling of the assessed chemical and choice of ECOSAR class is therefore considered to be conservative based on the information provided.

Endocrine effects/activity

While some UV filters have indications of endocrine effects, no information is currently available for the assessed chemical or structural analogues of the chemical.

Predicted no-effect concentration (PNEC)

A predicted no-effect concentration (PNEC) of 16 µg/L was calculated for the assessed chemical in the aquatic environment. This value was derived using the lowest predicted acute toxicity endpoint for green algae (calculated 96 h EC50 = 1.6 mg/L). An assessment factor of 100 was applied to this endpoint as experimental acute toxicity data was provided for all three trophic levels and predicted acute toxicity data was available for aquatic algae (EPHC 2009).

A PNEC for microorganisms was not calculated as the acute toxicity endpoint indicates the assessed chemical is not harmful to these organisms.

Categorisation of environmental hazard

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

Persistence

Persistent (P). Based on measured hydrolytic stability and lack of measured biodegradation during screening tests, the assessed chemical is categorised as persistent.

Bioaccumulation

Not bioaccumulative (not B). Based on a measured log K_{OW} value < 4.2, the assessed chemical has low bioaccumulation potential and is categorised as not bioaccumulative.

Toxicity

Not toxic (not T). Based on the available measured and calculated acute ecotoxicity endpoints above 1 mg/L, the assessed chemical is categorised as not toxic.

Environmental risk characterisation

The assessed chemical is persistent, but it is not bioaccumulative or toxic, according to Australian criteria. As such, the environmental risk may be estimated by the risk quotient method.

Based on the PEC and PNEC values determined above, risk quotients (RQ = PEC ÷ PNEC) have been calculated for release of the assessed chemical to river and ocean waters:

Compartment	PEC	PNEC	RQ
River	1.07 µg/L	16 µg/L	0.067
Ocean	0.107 µg/L	16 µg/L	0.007

For the diffuse ‘down the drain’ exposure scenario to Australian river and ocean waters, an RQ less than 1 indicates that introduction of the assessed chemical, in line with the terms outlined in this assessment certificate, is not expected to pose a significant risk to the environment. This is based on consideration of the environmental hazard characteristics and estimated releases.

Release of UV filters used in cosmetic sunscreen products from the skin of recreational water users is an additional environmental exposure pathway for the assessed chemical. While some UV filters have been detected in freshwater and ocean monitoring, no information is available for the assessed chemical or structural analogues of the chemical. Re-assessment/evaluation may be required if environmental monitoring information becomes available that indicates the presence of the assessed chemical above the calculated PNEC.

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