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

Octanamide, N-hydroxy-

Evaluation statement

22 December 2022

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AICIS evaluation statement

Subject of the evaluation

Octanamide, N-hydroxy-

Chemical in this evaluation

Name	CAS registry number
Octanamide, N-hydroxy-	7377-03-9

Reason for the evaluation

To evaluate information submitted by industry to meet their obligation in the terms of the Inventory listing.

Parameters of evaluation

The chemical, N-hydroxyoctanamide (CAS No. 7377-03-9), is listed on the Australian Inventory of Industrial Chemicals (the Inventory) with a specific requirement to provide information as a term of the Inventory listing.

The chemical was assessed in 2012 as a new industrial chemical in the limited notification category *under Section 23 of the Industrial Chemicals Notification and Assessment (ICNA) Act 1989* (NICNAS 2012).

The end-use concentration of the chemical was previously assessed up to a maximum of 0.5%, as a chelating agent for use in cosmetic and personal care products, and cleaning products. The assessment report indicated that the end use concertation of 0.3% would provide an adequate safety margin for repeated and concurrent use of cosmetic products containing the chemical. Therefore, a maximum concentration of 0.3% in the end use products was recommended in the assessment report.

Introducers have provided information under *Section 101 of the Industrial Chemicals Act 2019*.

New information indicated that the chemical was potentially being used at concentrations >0.3%. In addition, new hazard information has become available since the assessment in 2012, including sensitisation data and information on dermal absorption.

This evaluation is a human health risk assessment for all identified industrial uses of the chemical in Australia. This evaluation establishes concentrations in products introduced in Australia and considers all new information identified since the assessment in 2012.

This evaluation report should be read in conjunction with assessment report LTD1543 (NICNAS 2012).

Summary of evaluation

Summary of introduction, use and end use

Based on Australian and international use information the chemical is expected to have widespread and repeated use as chelating agent in cosmetic and personal care products, and domestic products. The chemical may also be distributed for professional use by hairdressers. Products containing the chemical may be applied by hand, applicators, or aerosols.

The chemical was previously assessed as being imported into Australia as a:

- blended bulk raw material at ≤20% for reformulation.
- component of finished cosmetic/personal care products at <0.5% concentration.

In Australia, the chemical has the following reported end-uses:

- chelating agent in leave-on and rinse-off cosmetic and personal care products (skin and hair products, and toiletry formulations)
- in cleaning wipes and furniture care products.

In Australia the chemical is mainly used at concentrations <0.3% in cosmetic and personal care products. The chemical had reported use in liquid foundation and make-up remover at a maximum of 0.6%.

The reported uses in Australia are consistent with uses described internationally.

Human health

Summary of health hazards

The critical health effects of N-hydroxyoctanamide for risk characterisation include:

- skin sensitisation
- haematological effects following repeated dermal exposure.

It is likely that the chemical will be absorbed through the skin due to its low molecular weight, potential surface activity and irritancy potential. In an in vitro study, dermal penetration of the chemical was greatest with the oil-in-water suspension with a total absorbed dose of 41.9%.

Available data suggest that the chemical has potential to cause skin sensitisation. Based on positive results from in chemico (Direct Peptide Reactivity Assay (DPRA: OECD 442C)) and 2 in vitro assays (ARE-Nrf2 luciferase test method (KeratinoSens™; OECD TG 442D) and the human cell line activation test (h-CLAT; OECD TG 442E)) that address specific events of the Adverse Outcome Pathway (AOP), the chemical is predicted to be a skin sensitiser.

The potential for skin sensitisation was supported by observations in humans. Results from human repeat insult patch test (HRIPT) studies demonstrated that the chemical could cause skin sensitisation. A weight of evidence (WoE) No Expected Sensitisation Induction Level (NESIL) of 1055.6 µg/cm^2 was calculated by the Cosmetic Ingredient Review (CIR) Expert Panel.

Positive patch test results were also reported in patients suspected of developing contact allergy following use of a moisturiser containing approximately 0.075%–0.15% N-hydroxyoctanamide. The positive results may have occurred due to impaired skin barrier function (compromised skin), or from the presence of chemicals that increase penetration.

N-hydroxyoctanamide is used as a chelating agent because it contains a hydroxamic acid functional group. Hydroxamic acids are known to inhibit certain enzymes such as urease (Bauer and Exner 1974) and, therefore, have been shown to have protein reactivity, an important factor in skin sensitisation potential.

Haematological effects including significant decreases in erythrocyte, haematocrit, and haemoglobin were observed in a 90 day oral repeated dose toxicity study at 2500 mg/kg bw/day using the chemical at 10% in lactose. The reported no observed adverse effect level (NOAEL) was 500 mg/kg for the chemical at 10% in lactose. Hence, the NOAEL for the chemical is 50 mg/kg bw/day. The haematological effects observed in this study are consistent with those observed with hydroxylamine and other hydroxylamine derivatives.

Based on the available data, the chemical:

- is expected to have low acute oral toxicity
- is expected to be non-irritating or slightly irritating to skin and eyes
- is not expected to have genotoxic potential
- was not teratogenic in a developmental study in rats.

The chemical may hydrolyse at high (>8) or low (<5) pH to form octanoic acid and hydroxylamine (NH_2-OH). The critical health effects of hydroxylamine include systemic long-term effects (haematological effects and carcinogenicity) and local effects such as irritation and skin sensitisation.

Hazard classifications relevant for worker health and safety

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

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction

Summary of health risk

Public

Based on available use information, there is potentially widespread public exposure as the chemical is present in various types of cosmetic and personal care products, and domestic products.

Available use information indicates that the public may be repeatedly exposed to the chemical by:

- direct application of the chemical to the body, face, or hair during use of cosmetic and personal care products
- incidental dermal and eye contact with the chemical during the use of domestic products
- inhaling aerosols/vapours during the use of cosmetic and personal care products.

The public risk is expected to be greatest through use of cosmetic and personal care products. The chemical is typically used at concentrations up to 0.3% in cosmetics, although use concentrations of up to 0.6% in certain make-up products have been reported in Australia.

The chemical is considered to be a skin sensitiser. Based on a quantitative risk assessment conducted by CIR using the WoE NESIL of 1055.6 µg/cm^2, the reported use concentrations in cosmetic and personal care products in Australia are considered acceptable. There may be increased risk of sensitisation in susceptible individuals, or in products where the chemical is formulated with chemicals that enhance penetration.

The chemical has potential to cause haematological effects following repeated exposure. The combined, worst case scenario internal dose from the chemical via dermal exposure was determined to be 0.286 mg/kg bw/day. Based on this value the calculated margin of exposure (MOE) for use of the chemical at 0.3% or the maximum reported concentration, in all categories of products when used simultaneously was 175. The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. Using interspecies and intraspecies assessment factors of 10, the acceptable MOE for NOAEL based assessment is considered to be 100 or greater.

The chemical is not expected to hydrolyse to hydroxylamine (NH_2-OH) at pH values likely to occur in formulated consumer products.

Overall, there are no identified risks that require risk management. If further information becomes available to indicate that the chemical is widely used at concentration levels >0.3%, risk management may be required.

Workers

During product formulation, packaging and distribution, dermal and ocular exposure to the chemical might occur at concentrations of up to 20%, particularly where manual or open processes are used during reformulation processes. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Potential inhalation exposure may also occur during these processes if aerosols are generated.

Worker exposure to the chemical at lower concentrations (up to 0.3%) could occur in workers using formulated products containing the chemical, such as hair salon professionals. The level and route of exposure will vary depending on the method of application and work practices employed.

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

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

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

Information relating to safe introduction and use

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

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

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

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

These control measures may need to be supplemented with:

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

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

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

Conclusions

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

Considering the proposed means of managing risks, the Executive Director is satisfied that when the chemical is introduced in accordance with the terms of the Inventory listing the human health risks can be managed within existing risk management frameworks. 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 and the proposed means of managing the risks identified during this evaluation are implemented.

The specific requirement to provide information as a term of the Inventory listing under *Section 101 of the IC Act* assists with managing the risks from introduction of the chemical. Given the identified uncertainty in the risks when the chemical is used in cosmetic and personal care products at concentrations >0.3%, the requirement to provide information is aligned with the risks identified in this evaluation statement. Therefore, the specific requirement to provide information as a term of the Inventory listing continues to apply to manage the risks from introduction of the chemical (see **Existing Australian regulatory controls** – AICIS section).

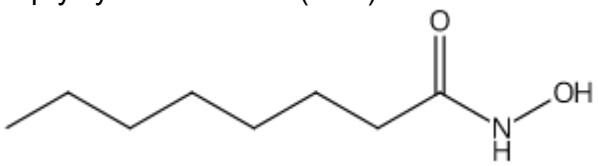
Note: Obligations to report additional information about hazards under Section 100 of the *Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Hydroxamic acids may exist in both keto and enol tautomeric forms. N-hydroxyoctanamide is an organic compound that, as depicted below, conforms to the keto form. The keto form predominates in acidic formulation, while enol will dominate under alkaline conditions (CIR 2020).

N-hydroxyoctanamide is used as a chelating agent because it contains a hydroxamic acid functional group. It is known that some bacteria can synthesise and use hydroxamic acid as iron scavengers or chelators (CIR 2020). N-hydroxyoctanamide can form strong complexes with oxidised transition metals and may react with oxidisers and acids. Complexation of the transition metal ions helps preserve cosmetic and personal care products.

Chemical name	Octanamide, N-hydroxy-
CAS No.	7377-03-9
Synonyms	N-hydroxyoctanamide; octanohydroxamic acid; caprylhydroxamic acid (INCI)
Structural formula	
Molecular formula	$C_8H_{17}NO_2$
Molecular weight (g/mol)	159.23
SMILES	O=C(NO)CCCCCCC
Chemical description	White to tan crystalline solid

Relevant physical and chemical properties

Physical form	Crystalline solid
Melting point	78.75 °C
Boiling point	343.32 °C
Vapour pressure	2.50 x 10^{-6} mm Hg (at 25 °C) (estimated)
Water solubility	1.55 g/L (at 23 °C)

pKa	9.56 ± 0.20 (predicted)
log K_{ow}	1.66 – 2.827

The chemical is stable under normal environmental conditions; however, it may hydrolyse to caprylic acid and hydroxylamine at extremely high or low pH. At high temperatures, the chemical can decompose to ammonia, and oxides of carbon and nitrogen.

Introduction and use

Australia

The chemical is not manufactured in Australia.

The chemical was originally assessed under the former National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2012). It had reported use as a bulk raw material imported at concentrations of <20% for reformulation into cosmetics and personal care products at final end-use concentrations of <0.5%. As a result of this assessment, a requirement to provide information in certain circumstances applies to the chemical (see **Existing Australian regulatory controls** section).

Following the listing of the chemical on the Inventory, information has been provided confirming the use of the chemical in cosmetic and personal care products, and domestic products. Several introducers advised the use of the chemical at concentrations higher than 0.3% in the following products, including:

- component of skin care products at concentrations up to 1%
- component of make-up remover at 0.5% and liquid foundation at 0.6%
- finished cleaning products (surface wipes) at concentrations of up to 0.35%.

A voluntary call for information under Section 75 of the *IC Act* was conducted to determine the specific product types and the concentration of the chemical in introduced products. The information provided confirmed that the chemical is mostly used in cosmetic and personal care products at concentrations <0.3%.

The Australian Society of Cosmetic Chemists (ASCC) position paper on “Preservatives Used in Personal Care Products” reports a recommended concentration of 0.05–0.15% when the chemical is used as a preservative (Williams 2018).

International

The chemical has widespread international use as a component of cosmetic products at a maximum concentration of 0.3% with reported function as a chelating agent (CIR 2020; DeLima Associates).

According to survey data from US Food and Drug Administration’s (FDA’s) Voluntary Cosmetic Registration Program (VCRP), the chemical is used in 269 formulations (198 leave on and 71 rinse off) in the following products (US FDA):

- body and hand products (≤0.25%)
- baby products including lotions, oils, and creams (≤0.15%)

- make-up preparations for application on or near the eye (≤0.2%)
- soap and detergent products that come into contact with mucous membranes (≤0.3%)
- aerosol and pump hair sprays (≤0.0075%).

Existing Australian regulatory controls

AICIS

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

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

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

The assessment report LTD/1543 prescribes the following circumstances under which the introducer must notify the Executive Director in writing within 28 days of changes to the introduction (Section 64(1) of the *ICNA Act*):

- the importation volume exceeds one tonne per annum notified chemical
- the notified chemical is used in cosmetic products at >0.3%
- the notified chemical is used in oral care products
- new information on the inhalation toxicity of the notified chemical becomes available.

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

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

Public

The chemical is listed in the Australian Therapeutic Goods (TGA) (Permissible Ingredients) Determination (No. 2) 2021 with the following requirements:

- only for use in topical medicines for dermal application and not to be included in medicines intended for use in the eye
- the concentration in the medicine must be no more than 0.5%.

Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (SWA).

International regulatory status

Exposure standards

No workplace exposure standards have been identified for this chemical.

United States of America

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of chemical used in cosmetic formulations as a chelating agent. The Panel concluded that the chemical is safe in cosmetics in present practices of use and concentration described in the safety assessment. The Panel cautioned against the use of the chemical in a manner that would result in increased dermal penetration (CIR 2020).

Human exposure

Public

There will be widespread and repeated exposure of the public to the chemical through the use of a wide range of cosmetic, personal care, and household products. The main route of exposure is expected to be dermal; however, inhalation exposure may occur from spray formulations. The chemical is not expected to be volatile due to its low vapour pressure.

Data on typical use patterns of product categories containing the chemical were derived from published sources (ACI 2010; Cadby et al. 2002; Loretz et al. 2006; SCCS 2021) and are shown in Table 1. For the purposes of public exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In calculating exposure estimates the following assumptions were applied:

- dermal absorption (DA) rate of 42% (see **Toxicokinetics** section)
- a lifetime average female body weight (BW) of 70 kg (enHealth 2012)
- concentration based on the maximum reported concentrations reported in Australia; otherwise, a concentration of 0.3%.

Table 1 Cosmetic and personal care products (dermal exposure)

Type of exposure	Product	Amount (mg/day)	C (%)	RF (unitless)	DA (%)	Daily systemic exposure (mg/kg bw/day)
Rinse-off skin & hair cleansing products	Shower gel	18670	0.3	0.01	42	0.0034
	Hand wash soap	20000	0.3	0.01	42	0.0036
	Shampoo	10460	0.3	0.01	42	0.0019
	Hair conditioner	3920	0.3	0.01	42	0.0007
Leave-on skin & hair care products	Body lotion	7820	0.3	1	42	0.1408
	Face cream	1540	0.3	1	42	0.0277
	Hand cream	2160	0.3	1	42	0.0389
	Deodorant (non-spray)	1500	0.3	1	42	0.0270
	Hair styling	4000	0.3	0.1	42	0.0072
Make-up products	Liquid foundation	510	0.6	1	42	0.0184
	Make-up remover	5000	0.5	1	42	0.0150
	Eye make-up	20	0.3	1	42	0.0004
	Mascara	25	0.3	1	42	0.0005
	Lipstick	57	0.3	1	42	0.0010
	Eyeliner	5	0.3	1	42	0.0001
Total		**75687**				**0.2864**

Daily systemic exposure = (A × C × RF × DA)/BW

(A = amount applied; C = chemical concentration; RF = retention factor; DA = dermal absorption; BW = body weight)

An aggregated daily systemic exposure of 0.286 mg/kg bw/day was calculated, with approximately 50% of this exposure from a single product type (body lotion) (see Table 1).

Health hazard information

Since the assessment of the chemical in 2012, new health hazard information has become available and is summarised below. Existing health hazard information for the chemical is reported in the assessment report LTD/1543 (NICNAS 2012).

Toxicokinetics

In vivo

Hydroxamic acid was not found in any tissues, except for the gastrointestinal tract following oral administration of 1-[^{14}C]N-hydroxyoctanamide (1.27 mg/kg) in rats. The radioactive chemical was found in the liver and the heart. Approximately 25% of the radioactive chemical was excreted as expired [^{14}C]CO_2 at 2 hours, while 6.9% and 0.6% were excreted in the urine and the faeces, respectively, within 24 hours. No other information was provided (CIR 2020).

In vitro dermal absorption

Dermal penetration of the chemical was estimated in an in vitro study using split-thickness human abdominal skin. 1-[^{14}C]N-hydroxyoctanamide was topically applied to the skin in 3 suspensions: oil-in-water, silicone-in-water, or clear lotion. The concentration of the chemical in each of the 3 suspensions was approximately 0.15% (w/w).

Dermal absorption of the chemical was reported to be highest with the oil-in-water suspension, followed by the silicone-in-water suspension, and then the clear lotion. The total absorbed dose (cumulative receptor fluid + receptor chamber was) from each preparation was 41.89% (2971 ng equiv/cm^2), 31.75% (2747 ng equiv/cm^2), and 22.93% (1824 ng equiv/cm^2) of the applied dose, respectively (CIR 2020).

Acute toxicity

Oral

Based on the available data, the chemical has a low acute oral toxicity with reported median lethal dose (LD50) of >10700 mg/kg in rats and >8820 mg/kg in mice (CIR 2020; Chemwatch).

Corrosion/Irritation

Skin irritation

Based on the in vitro data using reconstructed human epidermis tissue containing keratinocytes, the chemical is not expected to be irritating to skin.

Under the conditions of the EpiDerm™ in vitro skin irritation guideline study (OECD TG 439), the chemical was predicted to be a non-irritant to skin. Tissue viability was 102.6% (CIR 2020).

Eye irritation

Based on the previously assessed in vitro bovine corneal opacity and permeability (BCOP; 20% chemical) guideline study (OECD TG 437) and MatTek EpiOcular MTT viability assay (neat chemical) (NICNAS 2012), the chemical is unlikely to cause significant eye irritation.

Sensitisation

Skin sensitisation

Based on the available data, the chemical has potential to cause skin sensitisation. Positive results were reported from 1 in chemico and 2 in vitro cell-based assays that address specific events of the Adverse Outcome Pathway (AOP). Based on the "2 out of 3" defined approach (OECD Guideline 497) the chemical is predicted to be a skin sensitiser, warranting classification. Based on the available data, it is not possible to determine the skin sensitisation potency sub-categorisation for the chemical.

The potential for skin sensitisation was supported by observations in humans. Human repeat insult patch test (HRIPT) studies demonstrated that the chemical could cause skin sensitisation with a NESIL of 1055.6 µg/cm^2. Patch test studies in dermatitis patients suggest potential induction at lower levels where the skin barrier is compromised.

In chemico/in vitro

Positive results were reported for the chemical when tested in all 3 key event assays of the AOP, the direct peptide reactivity assay (DPRA; OECD TG 442C), the ARE-Nrf2 luciferase test method (KeratinoSens™; OECD TG 442D) and the human cell line activation test (h-CLAT; OECD TG 442E). No study details are available, and it is not possible to determine the confidence of the predictions. However, the study authors indicated that the DPRA results showed low reactivity, which is consistent with less potent sensitisers (CIR 2020).

The above tests are part of Integrated Approach to Testing and Assessment (IATA) which address specific events of the AOP leading to development of skin sensitisation (OECD 2016). Thus, these tests are considered relevant for the assessment of the skin sensitisation potential of the chemical.

The chemical showed positive responses in all of the above 3 tests of the AOP for skin sensitisation, indicating a skin sensitisation hazard.

In silico

The chemical has no structural alerts for protein binding based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox v4.2).

Hydroxamic acids are known to inhibit certain enzymes, including urease, which facilitates specific protein binding interactions. Protein reactivity is a key factor in skin sensitisation potential; therefore, the skin sensitisation potential of the chemical cannot be ruled out (NICNAS 2012).

Observation in humans

A large number of HRIPT tests have been conducted using various cosmetic formulations containing the chemical. No reactions were observed at concentrations up to 0.76% (induction and challenge dose 380 µg/cm^2).

Two HRIPT were conducted using the neat chemical (98% powder) diluted in petrolatum. In 1 study with 95 subjects, no skin reactions indicative of sensitisation was observed with an induction and challenge concentration of 1.9% (1055.6 µg/cm^2). In another study with an

induction and challenge concentration of 3.8% (2111.1 µg/cm^2), 3 subjects (out of 104) had clear positive reactions on challenge day 3, indicative of skin sensitisation (CIR 2020).

The chemical was the subject of a study aiming to identify the cause of allergic contact dermatitis in patients using a particular moisturiser (Ackermann et al. 2017). For the majority of these patients the moisturiser was used to treat atopic dermatitis, other types of eczema, dry skin, or other skin diseases. The new moisturiser containing N-hydroxyoctanamide, phenoxyethanol and methylpropanediol as preservatives (Phenostat™) replaced the parabens contained in the old moisturiser. Phenostat™ is used in cosmetic products at concentrations between 0.8% and 1.2%. It is present in the new moisturiser at 0.75%, corresponding to 0.0075%-0.15% N-hydroxyoctanamide.

Thirty-nine patients with suspected contact allergy to the product were patch tested using the following:

- moisturiser containing the preservative agents, phenoxyethanol, or methylpropanediol
- a dilution series of a moisturiser containing phenoxyethanol, methylpropanediol, and N-hydroxyoctanamide (Phenostat™)
- a dilution series of N-hydroxyoctanamide or its potassium salt.

Twenty eczema patients without prior use of the product in the 2 years preceding the study and 13 healthy volunteers served as controls.

The patch tests were performed under occlusive conditions for 2 days, and scores were taken at patch removal, and at days 4 or 5.

The patch tests were conducted using Phenostat™ at up to 1.5% concentration, and in N-hydroxyoctanamide and its potassium salt at up to 3.2% concentration (Table 2). In patients treated with N-hydroxyoctanamide, positive reactions were reported at test concentrations ≥0.01%. Negative results were reported in subjects tested with the formulations containing parabens, or phenoxyethanol or methylpropanediol. All control subjects showed negative patch test results (Ackerman et al. 2017).

Table 2: Patch test results for dilution series of N-hydroxyoctanamide or its potassium salts, and Phenostat™, all tested in pet (Adopted from Table 1 of Ackermann L et al. 2017)

	N-hydroxyoctanamide and its potassium salts								Phenostat™			
Patch Test result	3.20%	1.00%	0.32%	0.10%	0.032%	0.01%	0.0032%	0.001%	1.50%	0.50%	0.15%	0.05%
+++	9	10	4	1	0	0	0	0	5	2	0	0
++	6	21	15	6	3	0	0	0	10	6	3	2
+	0	7	17	18	14	1	0	0	16	10	8	7
?+	1	1	2	10	6	3	1	0	4	10	8	0
Negative	0	0	1	4	16	8	6	7	3	10	18	30
IR	0	0	0	0	0	0	0	0	1	1	2	0
No. tested	16	39	39	39	39	12	7	7	39	39	39	39

IR, irritant reaction, ?+ doubtful reaction

The patch test reactivity was similar in intensity between the chemical and its potassium salt. It was concluded that N-hydroxyoctanamide was the contact allergen causing the onset of

dermatitis in the subjects, despite the relatively low end-use concentration of 0.075−0.15% of the chemical in the product. It was suggested that an impaired skin barrier function may increase the risk of contact sensitisation to the chemical, as indicated by test subjects having pre-existing dermatitis. The study notes that further investigation is warranted to determine if the other chemicals within the preservative mixture, such as the phenoxyethanol or methylpropanediol, may weaken the skin barrier and promote the dermal absorption of N-hydroxyoctanamide (Ackermann et al. 2017).

As a follow up, the chemical (1% pet.) was added to the epicutaneous preservative series conducted at Helsinki University Central Hospital (2017) in an effort to determine if there were any new cases of contact allergy. In total, 16 patients with a positive patch test reaction were identified (3 with a (++)-reaction and 13 with a (+) reaction). Twelve of the 16 patients had previously used the moisturiser. Of the remaining 4 patients, the use of products containing the chemical could not be identified, but make-up or hair products were suspected (Virtanen and Ackermann 2018).

Repeat dose toxicity

Oral

In the previously assessed 90 day repeat dose oral toxicity study in Wistar rats (NICNAS 2012), the following observations were reported in animals treated with 2500 mg/kg bw/day of the chemical at 10% in lactose:

- slowness in activity
- an increase in leukocyte count
- significant decreases in erythrocyte, haematocrit, and haemoglobin counts
- significant decreases in alanine aminotransferase, glucose, and potassium levels (in the male group only)
- a significant increase in spleen weights
- a significant decrease in adrenal weights (in males)
- mild atrophy of the epithelial cells of the renal glomeruli and haemosiderin deposits in the spleen.

Based on these effects the No Observed Adverse Effect Level (NOAEL) for the chemical was established as 50 mg/kg bw/day and the Lowest Observed Adverse Effect Level (LOAEL) was 250 mg/kg bw/day.

The haematological effects (observed in this study) are consistent with the aetiology of hydroxylamine (NH_2-OH) derivatives (NICNAS 2020). Hydroxylamine species can induce methaemoglobin formation, increase lipid peroxidation, cause glutathione (GSH) depletion and impair the activity of various redox-active enzymes. Hydroxylamine-mediated radical stress can result in haematoxicity, haemolysis, and perpetuation of oxidative damage (Evelo et al. 1998).

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation are the local effect of skin sensitisation, and systemic haematological effects.

Public risk

Skin sensitisation risk

A quantitative risk assessment for skin sensitisation was conducted by the CIR. Given that reported use concentrations in Australia are similar to those reported internationally, the conclusions of this risk assessment are considered applicable.

Based on the results from the HRIPTs (see **Skin sensitisation** section), the highest concentration tested with no positive responses to skin sensitisation (no observable effect level (NOEL)) was calculated to be 1055.6 µg/cm^2. The estimated LOAEL was calculated to be 2111.1 µg/cm^2. Therefore, a Weight of Evidence No Expected Sensitisation Induction Level (WoE NESIL) of 1056 µg/cm^2 was chosen for risk assessment.

Consumer exposure levels (CELs) for each product category were determined for the reported maximum concentrations of use for the chemical. The risk was then determined by evaluating the acceptable exposure level (AEL)/CEL ratio; ratios ≥ 1 provide an acceptable risk. Using a NESIL of 1056 µg/cm^2, AEL/CEL ratio values ranged from 1.0 (for baby lotions, oils, and creams, not powder) to 269.2 (for bath soaps and detergents). Based on the results of this QRA, the study authors stated that "formulation of these products at their maximal concentration of caprylhydroxamic acid would present a negligible risk of inducing skin sensitisation" (CIR 2020).

Systemic exposure risk

A Margin of Exposure (MOE) methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB 2003). Risk to human health was characterised by MOE methodology in the previous NICNAS assessment, but the availability of new dermal absorption data allows this risk to now be refined.

The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, a MoE value ≥100 is considered acceptable to account for intra- and inter-species differences.

The starting points for risk characterisation are external exposure levels estimated based on reported national and international use concentrations (See **Human exposure** section). The NOAEL for the chemical (50 mg/kg bw/day) was derived from a non-guideline repeat dose toxicity study (see **Repeat dose toxicity**).

The MOE methodology was used to characterise the public health risks from exposure through simultaneous use of all categories of cosmetic and personal care products.

The combined, worst-case scenario internal dose from the chemical via dermal exposure was determined to be 0.286 mg/kg bw/day (See **Human exposure** section; Table 1). Based on this value the calculated MOE was 175.

References

ACI (2010) *Consumer Product Ingredient Safety, Exposure and risk screening methods for consumer product ingredients*, 2nd edn, American Cleaning Institute, Washington DC.

Ackermann L, Virtanen H, Korhonen L, Laukkanen A, Huilaja L, Riekki, R and Hasan T (2017) 'An epidemic of allergic contact dermatitis caused by a new allergen, caprylhydroxamic acid, in moisturisers', *Contact Dermatitis* 77: 159-162

Bauer L and Exner O (1974) 'The chemistry of Hydroxamid Acids and N-Hydroxyimides', *Angew Chem Internat Edit* 13(6): 376-384

Cadby PA, Troy WR and Vey MG (2002), 'Consumer exposure to fragrance ingredients: providing estimates for safety evaluation', *Regulatory Toxicology and Pharmacology* 36: 246-252, doi:10.1006/rtph.2002.1581

CIR (Cosmetic Ingredient Review) (2020) *Safety Assessment of Carprylhydroxamic Acid as Used in Cosmetics,* CIR, accessed March 2022

DeLima Associates (n.d.) Consumer Product Information Database, DeLima Associates website, accessed May 2021

ECB (European Chemicals Bureau) (2003) *Technical Guidance Document on Risk Assessment*, ECB, accessed September 2022

enHealth (2012) *Australian Exposure Factor Guide*, companion document to: *Environmental Health Risk Assessment: Guidelines for assessing human health risks from environmental hazards*, EnHealth, Commonwealth of Australia

Evelo, CT, Spooren AA, Bisschops RA, Baars, LG and Neis, JM (1998), 'Two mechanisms for toxic effects of hydroxylamines in human erythrocytes: involvement of free radicals and risk of potentiation', *Blood Cells Mol Dis* 24(3): 280-295

Loretz L, Api AM, Barraj L, Burdick J, Davis DA, Dressler W, Gilberti E, Jarrett G, Mann S, Pan YHL, Re T, Renskers K, Scrafford C and Vater S (2006), 'Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant', *Food and Chemical Toxicology* 44: 2008-2018, doi:10.1016/j.fct.2006.06.029

Chemwatch (n.d.), *Galleria Chemica,* Chemwatch website, accessed March 2022

MatTek Life Sciences (2020) *Ocular Irritation Protocol: Neat Method (MTT ET-50)* For Use with EpiOcular™ Tissue Model (OCL-200)

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2012) *LTD/1543 Octanamide, N-hydroxy-,* AICIS website, accessed March 2022

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2020) *IMAP Group Assessment Report – Hydroxylamine and its salts: Human health tier II assessment*, NICNAS, accessed March 2022

OECD (Organisation for Economic Co-operation and Development) (2022) *Quantitative Structure-Activity Relationship Toolbox (Version 4.2)* [Computer software], OECD, accessed September 2022

OECD (Organisation for Economic Co-operation and Development) (2016) *Guidance document on the reporting of defined approaches and individual information sources to be used within integrated approaches to testing and assessment (IATA) for skin sensitisation*, OECD, accessed September 2022

SWA (Safe Work Australia) (n.d.) *Hazardous Chemical Information System*, SWA website, accessed March 2022

SCCS (2021) 'The SCCS's notes of guidance for the testing of cosmetic substances and their safety evaluation', 11th revision, Scientific Committee on Consumer Safety, European Commission

Virtanen H, Ackermann L. Posters: P-058. Contact allergy from caprylhydroxamic acid - follow-up. *Contact Dermatitis.* 2018; 79:80

Williams R (2018) *Preservatives Used in Personal Care Products*, Australian Society of Cosmetic Chemicals website, accessed September 2022

TGA (Therapeutic Goods Administration) (n.d.) *Australian Approved Names List for Therapeutic Substances*, TGA, accessed March 2022

UNECE (United Nations Economic Commission for Europe) (2017) *Globally Harmonized System of Classification and Labelling of Chemicals (GHS), 7th Revised Edition*, UNECE, accessed March 2022

US FDA (United States Food and Drug Administration) (n.d.) *Voluntary Cosmetic Registration Program* (VCRP), US FDA website, accessed September 2022