File No: STD/1374

October 2010

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Alpha Glucosyl Hesperidin

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of Sustainability, Environment, Water, Population and Communities.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This Full Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

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FULL PUBLIC REPORT

The notifier has submitted with the application an assessment of the chemical by a notification and assessment scheme in an OECD country (United Kingdom). The health and environment hazard assessment of the United Kingdom reports were provided to NICNAS and where appropriate used in this assessment report. The other elements of the risk assessment and recommendations on safe use of the notified chemical were carried out by NICNAS.

Alpha Glucosyl Hesperidin

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Hayashibara International Australia Pty Limited (ABN 61 120 127 488)
Level 31 RBS Tower
88 Phillip Street
Sydney NSW 2000

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: means of identification, purity, impurities and use details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: density, vapour pressure, hydrolysis as a function of pH, adsorption/desorption, dissociation constant, autoignition temperature, explosive properties, acute toxicity to fish, acute toxicity to *Daphnia* and algal growth inhibition.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
UK

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Glucosyl Hesperidin (INCI name)
Alpha Glucosyl Hesperidin

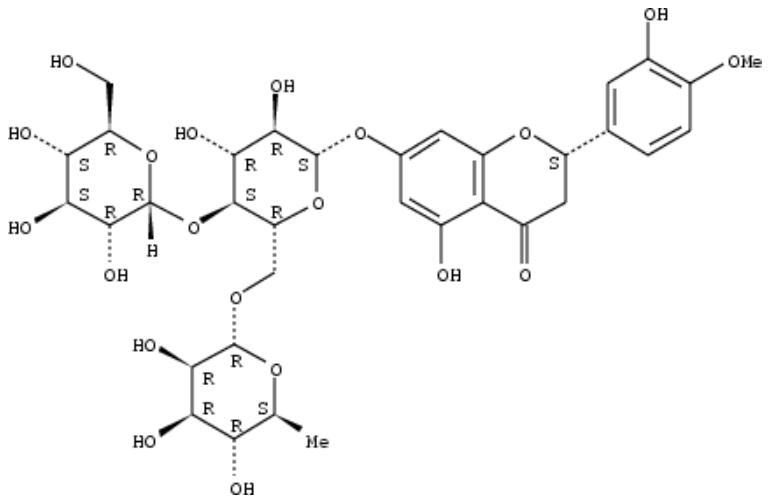
OTHER NAME(S)
Enzymatically Modified Hesperidin
Alpha G Hesperidin
4G-Alpha-D-Glucopyranosyl-Hesperidin
Glucosyl-Vitamin P

CAS NUMBER
161713-86-6

CHEMICAL NAME
4H-1-Benzopyran-4-one, 7-[(O-6-deoxy-α-L-mannopyranosyl-(1→6)-O-[α-D-glucopyranosyl-(1→4)]-β-D-glucopyranosyl)oxy]-2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-, (2S)-

MOLECULAR FORMULA
$C_{34}H_{44}O_{20}$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
772.71 Da

ANALYTICAL DATA
Reference NMR, IR, HPLC and UV/Vis spectra were provided.

3. COMPOSITION

DEGREE OF PURITY > 75%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Light yellow to yellowish brown powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	Decomposes at > 62°C	Measured
Boiling Point	Decomposes at > 62°C	Measured
Density	Not determined	Soluble powder
Vapour Pressure	Not determined	Estimated to be low based on the high molecular weight.
Water Solubility	> 543 g/L at 20°C	Measured by the flask method of OECD TG 105 (as stated in the Health and Safety Executive (UK) report)
Hydrolysis as a Function of pH	Not determined	The notified chemical may slowly hydrolyse in the environmental pH range (4–9)
Partition Coefficient (n-octanol/water)	log K_{ow} < -3.2 at 20°C	Estimated by the ratio of solubilities in water and n-octanol (Health and Safety Executive (UK) report)
Adsorption/Desorption	Not determined	The notified chemical is expected to be mobile in soils based on its high water solubility
Dissociation Constant	pK_{a1}, pK_{a2} = 10.0 ± 0.2	Analogue data (refer to Appendix A)
Particle Size	Not determined	Soluble powder
Flash Point	Not determined	Expected to be high based on the measured flammability.
Flammability	Not highly flammable	Measured
Autoignition Temperature	Not determined	Not expected to autoignite under

Explosive Properties	Not expected to be explosive	normal conditions of use. The structural formula contains no explosophores.

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties, refer to Appendix A.

Reactivity
The notified chemical is stable under normal use conditions and compatible with other cosmetic substances under normal usage conditions except at high pH.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be imported as a component (≤ 5%) in finished cosmetic products and as a raw material for reformulation.

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	1	2	2	5	5

PORT OF ENTRY
The notified chemical as a raw material will be imported into Port Botany, Sydney. Finished products containing the notified chemical will be imported by cosmetic companies into mainly Port Botany, Sydney and Port Melbourne.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in 1 kg net laminated multilayer bags.
The finished products containing the notified chemical will be imported in a variety of cosmetic containers suitable for sale and will be transported in a container from the wharf to the notifier's central warehouse by road.

USE
The notified chemical will be used as a humectant, skin conditioning agent, warming agent or antioxidant and added to cosmetic products and bath salts at a level of up to 5%.

OPERATION DESCRIPTION
The notified chemical will not be manufactured within Australia. When the notified chemical is imported in finished products they will be warehoused before distribution to customers.

Reformulation
When imported as a raw material the notified chemical will undergo quality assurance tests prior to being reformulated into cosmetic products. The notified chemical will then be weighed before being manually added to the mixing tank. The mixing facilities are expected to be fully automated, well ventilated (local exhaust ventilation) and closed systems. After being reformulated, the mixture containing the notified chemical at concentrations up to 5% will undergo further quality assurance tests before being packaged into containers.

End use
The finished cosmetic products containing the notified chemical will be used by the public and may also be used occupationally by beauticians. Depending on the nature of the product these could be applied in a number of ways such as by hand or using an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and Storage	10	4	12
Professional compounder	1	8	12
Chemist	1	3	12
Packers (Dispensing and Capping)	2	8	12
Store Persons	2	4	12
End Users	3×10^5	8	365

EXPOSURE DETAILS

Transport and warehousing

It is expected that transport and warehouse workers handling the imported raw material will only be exposed to the notified chemical in the event of spills due to an accident or as a result of a leaking bag. Following reformulation into cosmetic products, transport, warehouse and retail workers handling products will be exposed to concentrations of up to 5% notified chemical in the case of an accident when packaging is breached. The main route of exposure in these situations will be dermal although inhalation exposure to the powder is also possible.

Reformulation

During reformulation, dermal, ocular and inhalation exposure to the notified chemical may occur when weighing and transferring of the powder to the mixing tank. Local exhaust ventilation is expected to be in place to reduce exposure to dusts during this stage of the reformulation process. It is expected that negligible exposure will occur during the fully automatic and closed blending process. Workers involved in the reformulation process are expected to wear impermeable gloves, goggles or face shield and protective clothing to further minimise exposure. Exposure to the notified chemical at concentrations up to 5% during transfer of the formulated product to packaging is expected to be low due to the largely automated processes.

End use

Beauticians will be exposed to cosmetic products containing the notified chemical (≤ 5%) during application of the products to their clients. The main route of exposure is expected to be dermal, although ocular exposure to splashes is possible. PPE is not expected to be worn, however good hygiene practices are expected to be in place.

6.1.2. Public exposure

The general public will be repeatedly exposed to the notified chemical at concentrations up to 5% via a number of different consumer products.

Exposure to the notified chemical will vary depending on individual use patterns. The greatest exposure to the notified chemical is likely to be during the use of leave on products. In a worst case scenario when used as a body lotion, exposure of up to 8 g of product containing the notified chemical at a concentration of up to 5% will be considered per day to estimate systemic exposure (SCCP, 2006). Assuming a dermal absorption of 100% and a retention factor of 1, the maximum systemic exposure to the notified chemical is expected to be 6.7 mg/kg bw/day for a 60 kg person.

Public exposure from transport, storage, reformulation or disposal is considered to be negligible.

6.2. Human health effects assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Phototoxic potential	no evidence of phototoxicity
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Guinea pig, skin photosensitisation – adjuvant test.	evidence of photosensitisation
Rat, repeat dose oral toxicity – 90 days.	NOAEL > 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro Mammalian Chromosomal Aberration Test.	non genotoxic
Genotoxicity – in vivo mouse micronucleus assay	non genotoxic

Toxicokinetics, metabolism and distribution.
There are no toxicokinetic data on the notified chemical. The notified chemical has a molecular weight of 772.71 Da and a water solubility of > 543 g/L at 20°C and partition coefficient of log K_{ow} < -3.2 at 20°C. The moderately high molecular weight and hydrophilicity of the notified chemical suggest that absorption across the lipid rich environment of the stratum corneum into the epidermis would be slow and absorption across the gastrointestinal tract would be limited. The latter is supported by the absence of toxic effects in the acute and repeat dose toxicity tests with high NOAELs.

Acute toxicity.
The notified chemical is considered to be of low acute toxicity via the oral route based on tests conducted in rats. No acute dermal or inhalation toxicity data were provided.

Irritation and Sensitisation.
Based on a test conducted in rabbits the notified chemical is considered to be non-irritating to the skin and slightly irritating to the eye. The notified chemical was not a skin sensitiser in a guinea pig maximisation test. Slight skin irritation was seen in the phototoxicity test on guinea pigs at concentrations > 15%.

The notified chemical was found to produce no evidence of phototoxicity under the conditions of the test that was performed. The notified chemical produced evidence of photosensitisation under the conditions of the test at concentrations > 10%. No evidence of photosensitisation was observed at concentrations of the notified chemical at 1, 5 and 10% in water.

Repeated Dose Toxicity (sub acute, sub chronic, chronic).
Oral administration of the test material to rats through their food for a period of 90 consecutive days at nominal dose levels of 300, 1000 and 3333 mg/kg/day resulted in minimal centrilobular cellular hypertrophy observed in 2 males at the highest dose level. Therefore, the No Observed Adverse Effect Level (NOAEL) was established as > 1000 mg/kg bw/day in this study.

Mutagenicity.
The notified chemical was found to not be mutagenic using a bacterial reverse mutation test, and was not clastogenic in an *in vitro* mammalian chromosomal aberration test using Chinese hamster lung cells or a mouse micronucleus test. There was no indication in the micronucleus test that the chemical had reached the bone marrow even with the highest concentration of 2000 mg/kg bw.

Health hazard classification
Based on the data provided the notified chemical is not classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). The notified chemical did show evidence of photosensitisation at concentrations > 10%, however the Approved Criteria does not provide classification criteria or a risk phrase for this effect.

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Based on data provided the notified chemical is a slight skin and eye irritant and has the potential to be a photosensitiser at concentrations above 10%. The risk of systemic effects (excluding photosensitisation) is expected to be low based on the moderately high molecular weight and hydrophilicity of the notified chemical and the absence of effects seen in the repeat and acute oral toxicity tests. The notified chemical was also found to not be mutagenic or genotoxic.

The notified chemical will be introduced as a powder with an unknown particle size and hence a portion may be respirable. The notified chemical has a molecular weight of 772.71 Da and is water soluble and therefore if inhaled at low levels, it is likely to be cleared from the upper respiratory tract readily through mucociliary action. Small proportions of the notified chemical may reach the lower respiratory tract, but it should still be readily cleared from the lungs unless high levels are inhaled. When high concentrations of the notified chemical are inhaled, it is likely to be cleared from the lungs, but this may be slower and temporary respiratory impairment is possible. The expected use of dust masks and local exhaust ventilation when handling the powdered notified chemical by reformulation workers should reduce inhalation exposure levels and hence lower the risk of temporary lung overloading.

Although reformulation workers will handle the neat notified chemical, exposure is expected to be low given the proposed use of PPE and largely enclosed, automated processes used in reformulation facilities. Overall, the risk to the occupational health and safety of reformulation workers is not considered unacceptable, due to the expected low exposure to the notified chemical.

Beauticians will be exposed to cosmetic products containing the notified chemical (≤ 5%) during application of the products to their clients. As the notified chemical will be present in the finished products at a maximum concentration of 5%, which is less than the level (10%) in the photosensitisation study at which no evidence of sensitisation was observed the risk of photosensitisation is expected to be low. Although beauticians are not expected to use PPE considering the low hazardous nature of the notified chemical at the concentrations they will be exposed to, the risk to these workers is not considered unacceptable.

6.3.2. Public health

The general public will be repeatedly exposed to the notified chemical via a number of different consumer products, applied to the skin.

Local effects

The notified chemical is a slight skin and eye irritant. However, the notified chemical will be present in cosmetic products at concentrations ≤ 5% and therefore the risk of irritancy in consumers is not expected.

Systemic effects

A worst case systemic exposure of up to 6.7 mg/kg bw/day was estimated assuming 100% dermal absorption and a 60 kg body weight when using body lotions. Based on the NOAEL of 1000 mg/kg bw/day the MOE is expected to be 149. An MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

The notified chemical is a photosensitiser, however it will be present in the finished products at a maximum concentration of 5%, which is less than the level (10%) used in the photosensitisation study at which no evidence of sensitisation was observed. Therefore the risk of photosensitisation is expected to be low.

The risk to the public following exposure via consumer products is not considered to be unacceptable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of finished cosmetic products and will also be imported in neat form for blending. The notified chemical is expected to be released to landfill as residue in containers (estimated to be up to 1% of the annual import volume) and released to sewer from the cleaning of blending equipment (up to 3%).

Accidental spills during transport or reformulation are expected to be collected with inert material and sent to landfill.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be used as a component in cosmetic products and in bath salts. Therefore, it is expected that the majority of the imported quantity of notified chemical will be released to sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

Expired wastes and residue of the notified chemical in the empty containers (1%) is likely either to share the fate of the container and be disposed of to landfill, or to be washed to sewer when containers are rinsed before recycling.

7.1.2 Environmental fate

The majority of the notified chemical is expected to be released to the sewer as a result of its use pattern. The notified chemical is readily biodegradable (95% degradation within 7 days by OECD TG 301 A) and is predicted to be degraded by sewerage treatment plant (STP) processes by up to 67% (SimpleTreat; European Commission, 2003). Based on its high water solubility, the notified chemical is not likely to adsorb to sludge, nor is it likely to bioaccumulate in aquatic organisms. Primary degradation and hydrolysis of the notified chemical may form products with very low water solubilities. These products are expected to adsorb to sludge and thus be removed from the water phase during STP processes.

If released to surface waters, the notified chemical is expected to disperse and degrade. A small percentage of the notified chemical may be disposed of to landfill as expired waste or as residues in empty containers. In landfill, the notified chemical is likely to be mobile, however, it is also expected to rapidly degrade. The notified chemical will degrade biotically and abiotically to form water and oxides of carbon.

7.1.3 Predicted Environmental Concentration (PEC)

Assuming that most of the notified chemical will be washed into the sewer, the following predicted environmental concentration (PEC) in sewage effluent on a nationwide basis was calculated.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	5,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	5,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	13.70	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	21.161	million
Removal within STP	0%	
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	3.24	µg/L
PEC - Ocean:	0.32	µg/L

The notified chemical is readily biodegradable and significant removal of the chemical from influent by sewage treatment plant (STP) processes is predicted. However, in this worst case model, the majority of the

notified chemical is assumed to be released in effluent. STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 3.237 µg/L may potentially result in a soil concentration of approximately 21.58 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 107.9 µg/kg and 215.8 µg/kg, respectively. However, due to the biotic and abiotic degradability of the notified chemical, these calculated values represent maximum concentrations only.

7.2. Environmental effects assessment

No experimental ecotoxicological data were submitted. The modelled endpoint estimates (ECOSAR (v1.00), Phenols, poly SAR; US EPA, 2009) for the notified chemical are tabulated below.

Endpoint	*Predicted Result*	*Assessment Conclusion*
Acute toxicity		
Fish	LC50 (96 h) >> 100 mg/L	Not harmful to fish
Daphnia	EC50 (48 h) >> 100 mg/L	Not harmful to aquatic invertebrates
Algae	EC50 (96 h) = 25.0 mg/L	Harmful to algae
Chronic toxicity		
Fish	ChV‡ (30 d) >> 100 mg/L	Not harmful to fish
Daphnia	ChV‡ (21 d) >> 100 mg/L	Not harmful to aquatic invertebrates
Algae	ChV‡ > 100 mg/L	Not harmful to algae

‡ ChV (Chronic Value) = $(LOEC \times NOEC)^{½}$

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) the notified chemical is considered to be not harmful to fish and aquatic invertebrates but is classified as harmful to algae. On the basis of the acute algal toxicity, the notified chemical is formally classified as 'Acute Category 3; Harmful to aquatic life.' As the notified chemical is readily degradable and the chronic endpoints indicate no long term harmful effects to aquatic biota, the notified chemical is not classified for long term hazard.

7.2.1 Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the estimated acute algal endpoint for the notified chemical and an assessment factor of 1000. Although endpoints are available for three different trophic levels, the notified chemical contains structural complexity that may not be fully accounted for by the most representative SAR (Phenols, poly) and, as there are no available analogue data to support these predictions, the most conservative assessment factor of 1000 is applied in this case.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Alga)	25.0	mg/L
Assessment Factor	1,000	
PNEC:	25.0	µg/L

7.3. Environmental risk assessment

Based on the above PEC and PNEC values, the following Risk Quotient (Q) has been calculated:

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	3.24	25	0.129
Q - Ocean:	0.32	25	0.013

The majority of the notified chemical will be disposed of to the sewer, however it is expected to degrade during sewage treatment plant processes. The notified chemical is unlikely to persist in surface waters if released in treated effluent and has a low potential for bioaccumulation. The risk quotient (PEC/PNEC) for the conservative worst case scenario of unmitigated release of the notified chemical to surface waters in treated effluents is below 1 for both riverine and oceanic discharge scenarios. Therefore, the notified chemical is not expected to pose a risk to the environment when used as described.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the data provided the notified chemical is not classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

The classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	***Hazard statement***
Aquatic environment	Acute Category 3	Harmful to aquatic life

Human health risk assessment
Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unacceptable risk to the health of workers.

When used in the proposed manner, the notified chemical is not considered to pose an unacceptable risk to public health.

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not expected to pose a risk to the environment.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - Local exhaust ventilation

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - Avoid skin and eye contact
  - Avoid inhalation of dusts

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure during handling of the notified chemical for formulation of products:
  - Respiratory protection (i.e. dust masks)
  - Gloves
  - Overalls

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

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act; if
- the function or use of the notified chemical has changed from a component of cosmetic products and bath salts at a level of up to 5%, or is likely to change significantly;
- the amount of chemical being introduced has increased from 5 tonnes, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet
The MSDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point Decomposes without melting at > 62ºC

Method	OECD TG 102 Melting Point/Melting Range. EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Decomposed at temperatures > 62ºC No significant protocol deviations. GLP compliant.
Test Facility	RCC (2005c)

Boiling Point Decomposes without boiling at > 62ºC

Method	OECD TG 103 Boiling Point. EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	Decomposed at temperatures > 62ºC No significant protocol deviations. GLP compliant.
Test Facility	RCC (2005c)

Dissociation Constant pK_{a1}, pK_{a2} = 10.0 ± 0.2

Method	The pK_as of an analogue chemical (hesperidin) were measured by capillary electrophoresis. The ionisation constants were determined by non-linear regression fitting of a sigmoidal curve to the effective mobility of the test substance against pH.
Remarks	The acid dissociation constants were measured for hesperidin. Hesperidin and the notified chemical are both glycosylated derivatives of the same flavanone, hesperitin. These glycosylated flavonoids both contain the same two weakly acidic phenols and hesperidin is therefore an acceptable analogue for the estimation of the dissociation constants for the notified chemical.
Test Facility	Serra et al. (2008)

Flammability Not highly flammable

Method	EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks	Could not be ignited with a flame during the preliminary test (contact time approximately 2 minutes). No significant protocol deviations. GLP compliant.
Test Facility	RCC (2005e)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (> 75%)
METHOD	OECD TG 401 Acute Oral Toxicity. EC Directive 92/69/EEC B.1 Acute Toxicity (Oral).
Species/Strain	Rat/HanIbm: WIST (SPF)
Vehicle	Water
Remarks - Method	GLP compliant No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5 per sex	2,000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity	There were no deaths. No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	Body weight gains were as expected.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	RCC (1997a)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical (> 75%)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 Males
Vehicle	Water
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	The powdered test substance (0.5 g) was moistened with water before being applied to the skin (6 cm^2) of the rabbits. GLP compliant No significant protocol deviations

RESULTS

Remarks - Results	A single 4-hour, semi-occluded application of the test material to the intact skin of the 3 rabbits produced no signs of irritation or corrosion. Reversible light yellow staining by the notified chemical on the skin at the test sight was observed.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	RCC (1999a)

B.3. Irritation – skin (Phototoxicity)

TEST SUBSTANCE Notified chemical (> 75%)

METHOD OECD Guidelines for Testing of Chemicals. Draft Proposal for a New Guideline: "Acute Dermal Photoirritation Dose-Response Test." February 1995.

Species/Strain Guinea Pig: Ibm:GOHI;SPF-quality Guinea Pigs.

Number of Animals 15 Female (10 test group; 5 control)

Vehicle Water

Observation Period 72 hours

Remarks – Method The right flank was used to evaluate the highest non-irritation concentration and hence no pre-test was conducted.

0.025 mL of the test substance at concentrations of 50, 25, 15 and 10% was applied to four 2 cm^2 sites on the left flank. After 30 minutes the left flank of the animals were exposed to non-erythematogenic UV-A irradiation (20 J/cm^2). The same procedure was repeated for the right flank but the test sites remained unexposed to light and served as control sites. The animals of the control group were treated with the vehicle alone. Animals were examined at 24, 48 and 72 hours.

Any skin reactions at an irradiated site of greater severity than those at a non-irradiated site were attributed to phototoxicity.

RESULTS

Lesion	*Mean Score**			*Concentration (%)*	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	24hr	*48hr*	*72hr*				
Test group							
Erythema							
- *Irradiated*	0.6	0.4	0.3	50	1	> 72 h	1
- *Non-irradiated*	0.5	0.3	0.2	50	1	> 72 h	1
- *Irradiated*	0.4	0	0	25	1	< 48 h	0
- *Non-irradiated*	0.3	0	0	25	1	< 48 h	0
- *Irradiated*	0	0	0	15	0	< 24 h	0
- *Non-irradiated*	0	0	0	15	0	< 24 h	0
- *Irradiated*	0	0	0	10	0	< 24 h	0
- *Non-irradiated*	0	0	0	10	0	< 24 h	0
Vehicle control							
Erythema							
- *Irradiated*	0	0	0	0	0	< 24 h	0
- *Non-irradiated*	0	0	0	0	0	< 24 h	0

*Calculated on the basis of the scores for ALL animals.

Remarks – Results The positive (8-methoxypsoralene) and vehicle controls gave satisfactory responses, confirming the validity of the test system.

There were no deaths during the course of the study and no necropsies were performed. The body weights of animals during the treatment period remained within the normal range except for one rat that lost weight and another rat who failed to gain weight.

No clear difference was observed between the non-irradiated and the irradiated skin sites after treatment with the test substance at 50% and 25% in water. No signs of irritation were observed at the 15 and 10% concentrations or in the control animals.

CONCLUSION The notified chemical produced no evidence of phototoxicity under the conditions of the study.

TEST FACILITY RCC (1998a)

B.4. Irritation – eye

TEST SUBSTANCE Notified chemical (> 75%)

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation).

Species/Strain Rabbit/New Zealand White
Number of Animals 3 Males
Observation Period 21 Days
Remarks - Method Conjunctival discharge was not measured.
No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0	0	1	2	< 14 Days	0
Conjunctiva: chemosis	0	0	0	0	< 1 hour	0
Corneal opacity	0	0	0	0	< 1 hour	0
Iridial inflammation	0	0	2	2	21 Days	2

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks - Results A single application of the test material to the non-irrigated eye of three rabbits produced mild conjunctival irritation. Two treated eyes appeared normal at the 24 hour observation with the remaining eye appearing normal at the 14 day observation.

In one animal the iridic light reflex was absent in all observation intervals from one hour until termination on day 21. This finding was not noted in any other animal at any observation interval and signs of irritation seen in this and the other remaining animals were considered to be minimal. Therefore the finding was considered to be incidental.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY RCC (1999b)

B.5. Skin sensitisation

TEST SUBSTANCE Notified chemical (> 75%)

METHOD OECD TG 406 Skin Sensitisation - Guinea Pig Maximisation Test.
EC Directive 96/54/EC B.6 Skin Sensitisation - Guinea Pig Maximisation Test.

Species/Strain Guinea pig/Himalayan spotted Ibm: GOHI; SPF
PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: < 1%
topical: 5%

MAIN STUDY
Number of Animals Test Group: 10 Control Group: 5

INDUCTION PHASE	Induction Concentration: intradermal: 5% topical: 50%
Signs of Irritation	Signs of irritation were seen in 9/10 of the test group animals during the induction phase.
CHALLENGE PHASE	
1st challenge	topical: 5%
Remarks - Method	No significant protocol deviations. GLP compliant.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test group	5%	0/10	0/10
Control group	5%	0/5	0/5

Remarks - Results	There were no deaths or substance-related signs of toxicity during the study. Temporary yellow staining was noted after topical application of the notified chemical. The positive control confirmed the sensitivity of the test system.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	RCC (1998b)

B.6. Photosensitisation

TEST SUBSTANCE	Notified chemical (> 75%)
METHOD	OECD Guidelines for Testing of Chemicals. Draft Proposal for a New Guideline: "Acute Dermal Photoirritation Dose Response Test." February 1995. CTFA Safety Testing Guidelines, The Cosmetic, Toiletry and Fragrance Association, Inc. Washington, D.C. 20036; "Guidelines for Evaluating Photodermatitis", 1991.
Species/Strain	Guinea pig/Ibm: GOHI SPF-quality
MAIN STUDY	
Number of Animals	Test Group: 20 Control Group: 10
Induction phase	Induction Concentration: Topical: 50% w/w in water
Signs of Irritation	Defined erythema and desquamation of the skin was observed.
CHALLENGE PHASE	
1st challenge	Topical: 15, 10, 5 and 1% w/w in water
Remarks – Method	The results of the phototoxicity study were used to select the test concentration for this study. Irritation was noted at 50 and 25% during the phototoxicity study and therefore a 15% concentration was chosen as the maximum non-irritant concentration for the present study. *Induction* Four intradermal injections of Freund's Complete Adjuvant (1:1 with physiological saline) were made followed by topically applied test substance (50%) to a skin area of 8 cm^2. The skin sites were then irradiated with UV-A light 10 J/cm^2 followed by UV-B light 1.8 J/cm^2.

The duration of exposure was regulated by a time control device which switched off immediately after reaching the registered dose. Topical application followed by irradiation was repeated a further 4 times on days 3, 4, 9 and 11.

Challenge
On day 22, the test material was applied to separate skin (2 cm^2) sites at concentrations of 15, 10, 5 and 1%. The skin sites were then irradiated with UV-A light 10 J/cm^2 only.

Any skin reactions at an irradiated site of greater severity than those at a non-irradiated site were attributed to phototoxicity.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*		
		24 h	*48 h*	*72 h*
Test Group	15% irradiated	6/20	3/20	0/20
	15% non-irradiated	0/20	0/20	0/20
	10% irradiated	0/20	0/20	0/20
	10% non-irradiated	0/20	0/20	0/20
	5% irradiated	0/20	0/20	0/20
	5% non-irradiated	0/20	0/20	0/20
	1% irradiated	0/20	0/20	0/20
	1% non-irradiated	0/20	0/20	0/20
Control Group	15% irradiated	0/10	0/10	0/10
	15% non-irradiated	0/10	0/10	0/10
	10% irradiated	0/10	0/10	0/10
	10% non-irradiated	0/10	0/10	0/10
	5% irradiated	0/10	0/10	0/10
	5% non-irradiated	0/10	0/10	0/10
	1% irradiated	0/10	0/10	0/10
	1% non-irradiated	0/10	0/10	0/10

Remarks - Results

The positive and vehicle controls gave satisfactory responses, confirming the validity of the test system.

There were no deaths during the course of the study and no necropsies were performed. No symptoms of systemic toxicity were observed in the animals. The body weights of animals during the treatment period remained within the normal range.

No skin reactions in the test group or the control group were observed in the animals treated with the test article at 1, 5 and 10% in water.
Defined erythema reactions were observed at the test site with 15% concentration in 6/20 animals in the test group at the 24 hour observation and 3/20 animals at the 48 hour observation which were irradiated.

CONCLUSION

The notified chemical was considered to produce evidence of photosensitization to guinea pig skin under the conditions of the study when applied at concentrations > 10%.

TEST FACILITY

RCC (1999c)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical (> 75%)
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain	Rat/HanRcc:WIST (SPF)
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	None, the notified chemical was added to the feed.
Remarks - Method	Three female animals from the mid dose group were excluded from the study after becoming pregnant. No significant protocol deviations. GLP compliant.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration mg/kg bw/day*			*Mortality*
		Nominal	*Actual (male)*	*Actual (female)*	
control	10 per sex	0	0	0	0/20
low dose	10 per sex	300	279	322	0/20
mid dose	10 per sex	1000	927	1064	0/20
high dose	10 per sex	3333	3084	3428	0/20

Mortality and Time to Death

There were no unscheduled deaths during the study.

Clinical Observations

There were no treatment related clinical signs noted during the study. There were no significant differences in the bodyweight gain and food consumption between the control and treated groups. Three rats presented with incidental findings: one male rat in the mid dose group had a white 35 mm nodule on the right flank from week 7 to 13; one male rat in the high dose group had a mass in the chest wall at week 10 but not found at necroscopy; and one female rat in the control group had hair loss on both shoulders and crusts on the left shoulder.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were no toxicologically significant test item related effects noted in the male and female rats treated at any dose.

Haemotology – In males in the high dose group reticulocytes were increased. In females in the high dose group lymphocytes and large unstained cells (LUCs) counts and the white blood cells were elevated. As the effects seen were within historical control values they are considered to be of no toxicological significance.

Clinical Biochemistry – In males in the mid and high dose groups the plasma sodium levels were slightly increased, the chloride levels in the mid dose group were minimally increased and the plasma phosphate levels in the high dose group were increased. In females in the high dose group the phosphorus levels were increased. As the effects seen were within historical control values they are considered to be of no toxicological significance.

Effects in Organs

There were no toxicologically significant test item related effects noted in the organs of the male and female rats treated with the test item. A range of macro- and microscopic findings were noted in individual animals including in the control group, however there was no dose response relationship seen and the findings were considered to be part of the normal background pathology of rats of this age and strain.

Organ Weights –Statistically significant reductions in the mean testes weights of males in the low and high

dose groups were observed, no significant reduction was seen in the mid dose group.

Macroscopic Findings – One male rat in the low dose group presented with seminal vessels that had many dark red foci 1mm in diameter. One male rat in the mid dose group had a gray-white, firm nodule (35 mm diameter) in the sub cutis of the right flank. One female rat in the control group had a pelvic dilation in the left kidney. One female rat in the low dose group had a pelvic dilution in the right kidney. One female rat in the high dose group had a yellowish firm nodule (2 mm diameter) in the uterine adipose tissue.

Microscopic Findings – Minimal centrilobular hepatocellular hypertrophy was observed in two male rats in the high dose group.

Remarks – Results

The study authors established the No Observed Adverse Effect Level (NOAEL) as > 3084 mg/kg bw/day for males and > 3428 mg/kg bw/day for females considering the hepatocellular hypertrophy seen in 2 males at the highest dose rate as an adaptive character. Considering the minimal centrilobular cellular hypertrophy observed in 2 males at the highest dose level, 1000 mg/kg bw/day was selected by NICNAS as the NOAEL.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as > 1000 mg/kg bw/day in this study, based on the presence of minimal centrilobular cellular hypertrophy in male animals at the higher dose rates tested.

TEST FACILITY RCC (2005f)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical (> 75%)

METHOD

	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 92/69/EEC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure and Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102. *E. coli*: WP2uvrA.
Metabolic Activation System	Rat S9 fraction from phenobarbitone/β-napthoflavone induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 33-5,000 µg/plate b) Without metabolic activation: 33-5,000 µg/plate
Vehicle	Water
Remarks - Method	Two main tests were conducted the first using the plate incorporation procedure and the second using the pre incubation procedure. No significant protocol deviations. GLP compliant.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1 (Plate)	> 5000	> 5000	> 5000	negative
Test 2 (Pre)		> 5000	> 5000	negative
Present				
Test 1 (Plate)	> 5000	> 5000	> 5000	negative
Test 2 (Pre)		> 5000	> 5000	negative

Remarks - Results The notified chemical was tested up to the maximum recommended dose level of 5000 µg/plate. No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test material, either with or without metabolic activation.

All the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY CCR (1997a)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical (> 75%)

METHOD Ministry of Health, Labour and Welfare. "Guidelines for designating of food additives and for revision of standards for use of food additives" Chapter V "The recommended method for safety study" Notification No 29, 22 March 1996 Japan.
Similar to the later OECD guideline TG 473 In vitro Mammalian Chromosomal Aberration Test.

Cell Type/Cell Line: Chinese Hamster Lung fibroblast cells (CHL/IU)
Metabolic Activation System: Rat S9 fraction from Aroclor 1254 induced rat liver.
Vehicle: Water
Remarks - Method: A dose finding test was performed in order to select appropriate test item dose levels for the chromosomal aberration test. The dose levels used were 0, 4.9, 9.8, 19.6, 39.1, 78.2, 156.3, 312.5, 625, 1250, 2500 and 5000 µg/mL. No cytotoxicity was found at any dose, regardless of the presence or absence of metabolic activation. Therefore, the highest dose for the main study was set at a concentration of 5000 µg/mL of the test substance.
The 24 hour continuous exposure study was only conducted in the absence of metabolic activation.
GLP compliant.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 4.9, 9.8, 19.6, 39.1, 78.2, 156.3, 312.5, 625, 1250*, 2500* and 5000*	6 h	24 h
Test 2	0*, 4.9, 9.8, 19.6, 39.1, 78.2, 156.3, 312.5, 625, 1250*, 2500* and 5000*	6 h	24 h
Present			
Test 1	0*, 4.9, 9.8, 19.6, 39.1, 78.2, 156.3, 312.5, 625, 1250*, 2500* and 5000*	24 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5000	> 5000	> 5000	negative
Test 2		> 5000	> 5000	negative
Present				
Test 1	> 5000	> 5000	> 5000	negative

Remarks - Results	The positive and vehicle controls gave satisfactory responses, confirming the validity of the test system. The test material did not induce any statistically significant increases in the frequency of cells with aberrations, or in the numbers of polyploid cells.
CONCLUSION	The notified chemical was not clastogenic to Chinese Hamster Lung cells treated in vitro under the conditions of the test.
TEST FACILITY	BioToxTech (2006a)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical (> 75%)
METHOD	Ministry of Health, Labour and Welfare. "Guidelines for designating of food additives and for revision of standards for use of food additives" Chapter V "The recommended method for safety study" Notification No 29, 22 March 1996 Japan. Similar to the later OECD guideline TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse, CrljBgi:CD1 (ICR), SPF Strain.
Route of Administration	Oral – gavage
Vehicle	Water
Remarks - Method	A range-finding study was conducted using 15 male mice at 5 dose levels (125, 250, 500, 1000 and 2000 mg/kg bw). Only male mice were treated in the main study. GLP compliant.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5 Male	0	24
II (low dose)	5 Male	500	24
III (mid dose)	5 Male	1000	24
IV (high dose)	5 Male	2000	24
V (positive control, M)	5 Male	2	24

M = mitomycin C.

RESULTS

Doses Producing Toxicity	No signs of clinical toxicity are noted at any dose level.
Genotoxic Effects	A statistically significant increase in micronucleated PCEs was not observed at any dose level. The positive control induced statistically significant increases in micronucleated PCEs.
Remarks - Results	All 5 animals from each treatment and control group were selected for bone marrow analysis. It was not possible to confirm that the notified chemical reached the bone marrow.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo Mammalian Erythrocyte Micronucleus Test.
TEST FACILITY	BioToxTech (2006b)

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