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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

L-Tyrosine methyl ester hydrochloride

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Street Address:	334 - 336 Illawarra Road MARRICKVILLE NSW 2204, 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
Chemicals Notification and Assessment

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Procter & Gamble Australia Pty Ltd (ABN 91 008 396 245)
320 Victoria Road Rydalmere NSW 2116

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:
Part B: Density, Vapour Pressure, Partition Coefficient, Adsorption/Desorption, Dissociation Constant, Particle Size, Flammability Limits, Autoignition Temperature, and Explosive Properties.
Part C: Acute Toxicity (Oral/Dermal/Inhalation), Repeated Dose Toxicity, In Vitro and/or In Vivo Genotoxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
None.

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
L-Tyrosine, methyl ester, hydrochloride

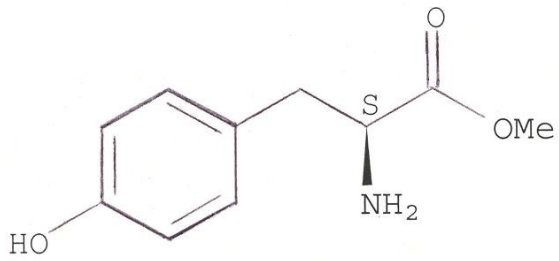
OTHER NAME(S)
Methyl tyrosinate HCl
Methyl L-tyrosinate hydrochloride
L-4-Hydroxyphenyl alanine methyl ester

MARKETING NAME(S)
L-Tyrosine methyl ester hydrochloride

CAS NUMBER
3417-91-2

MOLECULAR FORMULA
$C_{10}H_{13}NO_3$. HCl

STRUCTURAL FORMULA



• HCl

MOLECULAR WEIGHT
231.68

SPECTRAL DATA

METHOD	UV, IR, and NMR
Remarks	UV spectrum: λmax = 194 nm (C=O), ε = 1.3x10^4 L/mol/cm in water λmax = 224 nm (benzene), ε = 0.3x10^4 L/mol/cm in water λmax = 275 nm (benzene), ε = 0.4x10^3 L/mol/cm in water IR peaks: 3378 & 3342 (N-H stretch), 2944 (C-H stretch), 1743 (C=O), 1614, 1590 & 1513 (benzene stretch) cm^{-1} ^{1}H-NMR spectrum: 9.49, 8.64, 6.99, 6.71, 4.13, 3.65, 3.03 ppm ^{13}C-NMR spectrum: 169.50, 156.73, 130.41, 124.34, 115.45, 53.45, 52.56, 35.09 ppm.
TEST FACILITY	Nippon Rika (2004a)

3. COMPOSITION

DEGREE OF PURITY
>99%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)
None

ADDITIVES/ADJUVANTS
None

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
Import (as a finished hair conditioning product)

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.93	1.023	1.125	1.125	1.125

USE
A hair conditioning agent (max. 0.014%) in leave-on or rinse-off haircare formulations.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Procter & Gamble Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be transported by road as a component of finished haircare products in consumer size packages suitable for retail sale. For shipment, they will be packed in cardboard cartons.

5.2. Operation description

The haircare products containing the notified chemical will be shipped into Australia as finished formulations with approximately 12 shipments per year. No manufacturing, reformulating or repackaging of these products will occur in Australia.

Shipments of the notified chemical will be unloaded and loaded at dockside with the aid of cranes and forklifts. They will then transported to the notifier's warehouse at Arndell Park for storage and delivery to supermarkets, department stores, pharmacies or retail outlets for sale to consumer.

Consumers will wash and take care of their hairs by applying a shampoo, conditioner or a hair styling product two to seven times a weeks. It is expected that these haircare formulations will be rinsed-off or left on, and then be washed off at the next washing and end up in the sewer system.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Waterside and transport workers	50	8 hours/day	12 times/year
Warehouse workers	20-30	4 hours/day	100 times/year
Retail workers	10,000	1 hour/day	100 times/year

Exposure Details

The notified chemical is imported in final consumer use packages. Therefore, occupational exposure to the notified chemical will be limited to handling of the closed packages during transport, storage, retail distribution and sale. A large number of workers in these sectors will handle the products containing the notified chemical for brief periods, with no exposure expected except in the case of an accident. Should a spill occur, it is expected to be contained and absorbed with inert material (sand or vermiculate), and placed into properly labelled containers for disposal in accord with the MSDS and official regulations.

During normal shipment and handling it is anticipated that precautions will be taken to avoid accidental spillage. Transport and warehouse staff are expected to receive a training in the safe handling, transport, and storage of cosmetic products, good housekeeping practices, control of spillages and the correct use of equipment.

5.4. Release

RELEASE OF CHEMICAL AT SITE
No release of the notified chemical will occur within Australia as a result of manufacture or reformulation as the notified chemical is imported as finished haircare products. Release during transport and storage of the products containing the notified chemical is unlikely, with any spills of the notified chemical being limited by the small size of the import containers and the low level of the notified chemical within the formulations.

RELEASE OF CHEMICAL FROM USE
The total quantity of the notified chemical imported annually in haircare products will almost

completely be released to the aquatic environment through washing off from the hair. Dispersed release is expected throughout the continent to the sewerage systems of cities and towns.

5.5. Disposal

Residues in the consumer product containers may be disposed of to landfill via domestic garbage collection. However, the quantity of chemical finding its way into landfill is expected to be small due to the rinsing of empty containers and the increasing rate of collection empty containers for recycling.

5.6. Public exposure

Wide dispersive use with intermittent dermal contact and possibly accidental ocular contact with the notified chemical is expected to occur among public consumers. For purposes of estimating exposure, calculations are based on use information of rinse-off (eg shampoo and hair conditioner) and non rinse-off products (eg hair styling) as outlined in the Annex 5 of *the Notes of Guidance for Testing of Cosmetic Ingredients for their Safety Evaluation* (SCCNFP 2003), and assumptions that these haircare products are used extensively and contain a maximum of 0.014% notified chemical. The total daily exposure of an individual to the notified chemical is estimated to be (0.08 + 0.04 + 1) x 0.014% = 0.16 mg (not adjusted for body weight). Hence, systemic exposure dose = 0.16 mg/day x 100% skin absorption ÷ 60 kg = 0.003 mg/kg bw/day.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa White crystalline powder

Melting Point 188ºC

METHOD Japanese Pharmacopoeia 14 Melting Point - Method 1 (Capillary/Liquid Bath).
Remarks A capillary/liquid bath procedure (similar to OECD TG 102) was conducted in triplicates for three different lots of the notified chemical. It was observed for all samples that melting were began at ~187.5ºC with foaming accompanied at ~188ºC; then samples got dry and became a white mass. After that, no change was observed up to ~197ºC.
TEST FACILITY Nippon Rika (2004a)

Density 1194 kg/m^3 (predicted)

Remarks Density was calculated using the SPARC program (Hilal & Karickhoff 2003)

Vapour Pressure 1.64 x 10^{-7} kPa (predicted)

Remarks Vapour pressure was calculated using the SPARC program (Hilal & Karickhoff 2003)

Water Solubility 1670 g/L at 20±5ºC

Remarks Method of determination and analysis was not indicated. However, this solubility is defined as the degree of dissolution of the notified chemical within 30 min in water at 20±5ºC, with vigorous shaking for 30 sec every 5 min.
TEST FACILITY Nippon Rika (2004a)

Hydrolysis as a Function of pH

pH	*T (°C)*	*Hydrolysis (%)*
1 (HCl)	40	6.0 (24 h)
5.6 (acetate buffer)	40	18.3 (24 h)
5.6 (citrate buffer)	40	25.0 (24 h)
6.5 (water)	40	89.2 (24 h)
13 (NaOH)	40	90 (15 min)

Remarks Analytical method was HPLC. The notified chemical was most stable in acidic

solution, but rapidly hydrolysed in alkaline solution. In buffer solutions of pH range 4-6, the lower the pH the more stable the ester bonding of the notified chemical became. Also, it was observed that the notified chemical was more stable in acetate buffer solutions than in citrate buffer solutions.

TEST FACILITY Nippon Rika (2004b)

Partition Coefficient (n-octanol/water) log Pow = 0.55 (KowWin)
= 0.31 (Clog P)

Remarks The partition coefficient was calculated using two commercially available software packages, KowWin (US EPA) and Clog P (Daylight Chemical Information Systems Inc.). The calculated values based on these two packages' algorithms were within the experimental results (0.29 & 0.59) cited from their respective databases.

Adsorption/Desorption Not determined

Remarks The high water solubility of the notified chemical suggests it will stay in the water column, though some might adsorb to sediment, particularly in the cationic form.

Dissociation Constants pKa (-OH of tyrosine) = 10.5±1
pKa (-NH_2) = 7.09±0.3 (Hay & Porter 1967)
= 7.11 (SPARC, Hilal & Karickhoff 2003)
= 7.36±0.33 (ACDlabs pKa prediction ver 4.5)

Remarks Calculation documents were not provided.

Particle Size Not determined

Remarks The notified chemical will only be imported in aqueous formulations.

Flash Point Not applicable

Remarks The notified chemical is a solid at room temperature.

Flammability Limits Not determined

Remarks Not expected to be flammable (aqueous formulation).

Autoignition Temperature Not determined

Remarks The notified chemical melted and decomposed from 189.0ºC and from 265.6ºC on the observation of TG/DTA (thermogravimetry) chart, and is not expect to self ignite below its melting point.

Explosive Properties Not determined

Remarks The notified chemical is not expected to be explosive on structural ground. However it may be a dust explosion hazard in dry form.

Reactivity Stable under normal environmental conditions

Remarks By differential scanning calorimetry (DSC), the notified chemical was shown to have an endothermic peak due to decomposition at 189.3ºC. Thermal decomposition or burning may release noxious fumes such as oxides of carbon and nitrogen, and hydrogen chloride.

7. TOXICOLOGICAL INVESTIGATIONS

No acute, repeat dose, in vitro and/or in vivo genotoxicity data were available for the notified chemical. However, the notifier submitted the following toxicity information in relation to structural analogues of the notified chemical. Based on the chemical structure, the notified chemical would be expected to hydrolyse upon ingestion or dermal penetration to L-tyrosine and then to L-dopa (L-tyrosine, 3-hydroxy-). L-tyrosine is also a common constituent of the human diet, and L-dopa is a therapeutic agent for Parkinson's disease. L-tyrosine ethyl ester hydrochloride and DL-α-methyltyrosine methyl ester hydrochloride would be expected to be the closest related esters to the notified chemical.

	Result (LD50, mg/kg)			
Endpoint	*L-tyrosine (CAS no. 60-18-4)*	*L-Tyrosine, 3-hydroxy- (CAS no. 59-92-7)*	*L-Tyrosine ethyl ester HCl (CAS no. 4089-07-0)*	*DL-α-Methyltyrosine methyl ester HCl (CAS no. 7361-31-1)*
Acute	1450 (ip, mouse); low toxicity (rat & dog)	1780 (po, rat); low toxicity (mouse, rat & rabbit)	7710 (po, mouse); 13800 (po, rat)	400 (ip, mouse)
Repeat dose	25 mg/kg/day – 28 d (parenteral, rat & dog)	4 g/day – several yrs (Parkinson patients)	no data available	no data available
Genotoxicity	clastogenic	clastogenic	no data available	no data available

po = oral, ip = intraperitoneal. References: Neurology, May (Suppl):3, 1972; Toxicol Appl Pharmacol 28:1 & 227, 1974; J Pharm Soc Jap (Yakugaku Zasshi) 97:1117, 1977; Study of Medical Supplies (Iyakuhin Kenkyu) 18:474, 1987; Sax's Dangerous Properties of Industrial Materials, 9th ed, vol 1-3:1244, 1996; J Appl Toxicol 22:333, 2002; and Registry of Toxic Effects of Chemical Substances (RTECS) Database.

The toxicological endpoints submitted for the notified chemical are presented below:

Endpoint and Result	*Assessment Conclusion*
Acute oral	test not conducted
Acute dermal	test not conducted
Acute inhalation	test not conducted
Skin irritation – human	slightly irritating
Eye irritation – in vitro	irritating
Skin sensitisation – human	no evidence of sensitisation (0.1% notified chemical)
Repeat dose toxicity	test not conducted
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro	test not conducted
Genotoxicity – in vivo	test not conducted
Pharmacokinetic/Toxicokinetic studies	no data available
Developmental and reproductive effects	no data available
Carcinogenicity	no data available

7.1. Acute toxicity – oral

Remarks — Test was not conducted. The analogue L-tyrosine ethyl ester HCl (CAS no. 4089-07-0) showed low oral toxicity in rats and mice.

7.2. Acute toxicity – dermal

Remarks — Test was not conducted. The analogue L-tyrosine methyl ester (CAS no. 1080-06-4) has an estimated Kp value of 10^{-4} cm/h, which is indicative of relatively poor skin penetration potential. In addition, human patch tests (see below) showed no significant skin irritation and sensitisation with exposure levels higher than those expected from use of haircare products containing 0.014% notified chemical.

7.3. Acute toxicity – inhalation

Remarks	Test was not conducted. Inhalation exposure would be unlikely due to the expected low vapour pressure of the notified chemical.

7.4. Skin irritation – human volunteers

TEST SUBSTANCE	Shampoo ingredient mixtures containing 26.68% notified chemical
METHOD	Five Application Human Patch Test
Study Design	Five repeat, 24 h occlusive applications (three per week) of 0.5 mL test samples, after dilution with distilled water, containing 0.115% notified chemical to the intact upper arm skin (ie 144 µg/cm^2). The mean irritation index was calculated as the sum of individual scores at 48 h (or 72 h over the weekend period) for erythema and oedema, divided by the number of volunteers.
Study Group	37 volunteers (sex and age not reported)
Vehicle	Aqueous solution of amino acids and/or benzyl alcohol/isosteareth-20/polyquaternium-4.
Remarks – Method	An in house grading scale was used. This comprises 9 scores at 0.5 intervals from 0 to 4, eg 0 = no apparent cutaneous involvement, 0.5 = faint, barely perceptible erythema or slight dryness with glazed appearance, etc.
RESULTS	
Remarks – Results	The mean irritation indexes = 0.22, 0.23, and 0.25 (slightly irritating) for the different vehicles used, but no significant statistical differences were noted.
CONCLUSION	A five application human patch test was conducted under occlusive dressing using 0.115% notified chemical diluted with aqueous solutions of amino acids and/or benzyl alcohol/isosteareth-20/polyquaternium-4. The notified chemical was slightly irritating under the conditions of the test.
TEST FACILITY	IS Consultancy (1999)

7.5. Eye irritation – in vitro

TEST SUBSTANCE	A neat shampoo formulation containing 0.014% notified chemical
METHOD	Cytosensor Microphysiometer Bioassay (Parce et al. 1989).
Cell Type/Cell Line	MurineL929 fibroblasts
Vehicle	Serum- and NaH_2CO_3-free Dulbecco's Modified Eagle's Medium with 50 µg/mL gentamicin, 2 mM L-glutamine, and additional NaCl for consistent osmolarity (MDMEM).
Exposure Period	13.5 min
Test Concentration	0.0137, 0.0411, 0.123, 0.370, 1.11, 3.33, 10 mg/mL
Remarks – Method	The method measures test substance-induced alterations of the cellular acidification rate (ie the metabolic rate) in low buffer culture medium using a cytosensor microphysiometer. A dose range finding and at least two definitive tests were conducted with increasing test concentrations until either the highest dose is reached or the MRD50 (Metabolic Rate Decrement 50%) point has been surpassed. The study also consists of a solubility/miscibility test and a pH determination for the neat test sample and the highest concentration of the test sample in MDMEM.
RESULTS	
Remarks – Results	Mean MRD50 = 0.89 mg/mL for the samples containing the notified chemical, which was considered not significantly different from currently marketed benchmark formulations. Vehicle and positive (sodium lauryl

sulfate, MRD50 = 0.08 mg/mL) controls confirmed the validity of the assay.

CONCLUSION The notified chemical is irritating to the eye.

TEST FACILITY Institute for In Vitro Sciences (2003)

7.6. Skin sensitisation – human volunteers

7.6.1. Skin sensitisation – human volunteers (0.1% notified chemical)

TEST SUBSTANCE A hair treatment formulation containing 0.084% notified chemical

METHOD Human Repeat Insult Patch Test (Stotts 1980)

Study Design
Induction Procedure: Nine repeat, 24 h semi-occlusive applications (three per week) of 0.5 mL test samples to the intact upper arm skin (ie 105 µg/cm^2).
Rest Period: 14 days
Challenge Procedure: Single 24 h semi-occlusive applications on the original and alternate arms of subjects with minimal or no reactions during induction. Also, a phased challenge at 10, 25, 50, 75, and 100% of the test substance (applied concurrently with three other formulations, excluding some ingredients, and the perfume ingredient) was carried out on the backs of those subjects exhibiting significant reactions during induction to determine both the nature of the reactions and the causative agent. All applications were semi-occlusive except during the 3rd phased challenge.

Study Group 90 volunteers of either sex aged from 21-65 years

Vehicle Distilled water

Remarks – Method Due to unexpected strong skin reactions during induction, dressing was changed from occlusive to semi-occlusive after the second patch or after 4 days of the induction, and then patching was stopped after the fifth patch of the induction.

RESULTS

Challenge Concentration	*Volunteers Showing Skin Reactions (with Scores) after:*							
	Main challenge		*1st phased challenge*		*2nd phased challenge*		*3rd phased challenge*	
	48 h	*96 h*	*48 h*	*96 h*	*48 h*	*96 h*	*48 h*	*96 h*
100%	8/90 (1) 2/90 (2)	15/90 (1) 1/90 (2)						
10%	0/32	0/32						
25%	1/32 (1)	1/32 (1)						
50%			1/32 (1) 1/32 (2)*	1/32 (1) 1/32 (2)*				
75%					1/25 (1)	1/25 (1)		
100%							10/25 (1)	13/25 (1)

* This volunteer was not challenged at higher concentrations due to positive reactions (moderate erythema with papules). Six other volunteers were unable to continue participation for reasons unrelated to the test.

Remarks – Results
At the beginning of induction, volunteers developed significant skin reactions, with one noted with severe erythema, oedema and weeping evidence or bullous reaction after the second patch removal. 4/90 subjects still showed slight residual erythema (score 1) 10 days after the fifth patch termination.
At the arm challenge, a number of subjects showed typical irritation reactions with erythema, scaling and in some cases minor erosions were observed. An edge effect was a common observation but no true spreading reactions were observed. In most cases the reactions were more prominent on the original than the alternative arm.
There was little in the way of significant reactions observed to 10, 25, 50 and 75% concentrations, and apparently more effects when 100%

concentration of the test substance was used. This phenomenon would be expected to be present in both irritation and allergy. However a dermatologist's report attached to the study stated that the discrepancy between the degree of reactions when challenged on the back and on the arms during induction indicated the reactions are those of irritation rather than allergy. It also suspected that the most likely irritant is cetrimonium chloride ingredient and that the disassociation equilibrium of this quaternary ammonium compound has been altered by the addition of the amino acids with a resulting greater potential for irritation.

CONCLUSION A human repeat insult patch test was conducted using a hair treatment formulation containing 0.084% notified chemical under semi-occlusive dressing. There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test (0.1% notified chemical).

TEST FACILITY Inveresk Research (1999)

7.6.2. Skin sensitisation – human volunteers (0.001% notified chemical)

TEST SUBSTANCE A neat shampoo formulation containing 0.014% notified chemical

METHOD Human Repeat Insult Patch Test

Study Design Induction Procedure: Nine repeat, 24 h semi-occlusive applications (three per week) of 0.2 mL test samples at 10% dilution to the intact infrascapular back skin (ie 0.7 $\mu g/cm^2$).
Rest Period: 10-15 days
Challenge Procedure: Single 24 h semi-occlusive applications to sites previously unexposed to the test substance. Rechallenge was performed whenever there was evidence of possible sensitisation.
Skin reactions were evaluated after patch removal at 48 h (or 72 h over the weekend period) during induction, and at 48 h and 72 h at challenge.

Study Group 107 volunteers of either sex aged from 18-70 years (completed cases)

Vehicle Distilled water

Remarks – Method For a completed case, a subject must have 9 applications of the test substance and no fewer than 8 subsequent readings during induction, and a single application and 2 readings at challenge.

RESULTS

Remarks – Results There were no significant dermatological responses reported.

CONCLUSION A human repeat insult patch test was conducted using 10% dilution of a neat shampoo formulation containing 0.014% notified chemical under semi-occlusive dressing. There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test (0.001% notified chemical).

TEST FACILITY TKL Research (2003)

7.7. Repeat dose toxicity

Remarks Test was not conducted. Analogues showed low repeat oral dose toxicity. The notified chemical is also expected to readily hydrolyse to a normal dietary component.

7.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD JMHW Reverse Mutation Test using Microorganisms.

	Pre incubation procedure.
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100. *E. coli*: WP2uvrA.
Metabolic Activation System	S9 fraction from phenobarbital and 5,6-benzoflavone induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 5, 20, 78, 313, 625, 1250, 2500, 5000 µg/plate. b) Without metabolic activation: 5, 20, 78, 313, 625, 1250, 2500, 5000 µg/plate.
Vehicle	Distilled water
Remarks – Method	A single test was conducted in duplicate.

RESULTS

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

Remarks - Results	Neither dose-related nor two fold or more increase in revertant colonies compared with the vehicle control was observed in any bacterial strains at any dose levels in either the presence or absence of metabolic activation. The vehicle and positive controls responded appropriately.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	JBS Genetic Laboratory (2000)

7.9. Genotoxicity – in vitro

Remarks	Test was not conducted. A database search found that the analogues L-tyrosine and L-dopa are clastogenic in vitro. However, the meaning of these results in practice is not clear as a positive result was found for the nutrient, tyrosine.

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE	Methyl tyrosine
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I).
Inoculum	Activated Sludge Chemical Evaluation and Research Institute, Japan
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical oxygen demand (BOD) and dissolved organic carbon (DOC)
Remarks - Method	Samples were prepared at a loading rate of 100 mg/L of medium. The test was performed with 4 different solutions. These consisted of a reference compound with activated sludge and basal medium (single bottle), sludge and basal medium (single bottle), test material with sludge and basal medium (3 bottles) and test substance in water.

RESULTS

Test substance			*Aniline*	
Day	*% degradation*		*Day*	*% degradation*
	BOD	*DOC*		*BOD*
7	59	–	7	57
14	67.5		14	72
21	73		21	72
28	75	99	28	72

Remarks - Results The extent of degradation of the reference material validates the test.

CONCLUSION The test material is readily biodegradable under the conditions the test as > 60% was degraded within 10 days of reaching 10%.

TEST FACILITY Mitsubishi (2004)

8.1.2. Bioaccumulation

The bioaccumulation potential of the notified chemical was not investigated experimentally. The notifier provided modelling using the PBT Profiler (http://www.pbtprofiler.net) which indicates that the bioaccumulation potential of the notified chemical would be low (based on log P = -1 and a water solubility of 10 g/L. This is consistent with the high water solubility, low partition coefficient and high degree of ionisation (Connell 1989).

8.2. Ecotoxicological investigations

No experimental data on the aquatic toxicity of the notified chemical has been provided. The notifier has provided the results of quantitative structure activity relationship (QSAR) modelling for the deprotonated notified chemical using the US EPA ECOSAR program. These results, which are relevant at or above pH 8, are summarised below.

Functional Group	*End point*		
	Fish (LC50, mg/L)	*Daphnid (LC50, mg/L)*	*Green Algae (EC50, mg/L)*
Aliphatic Amines	429 (N= 55 R^2 0.82)[a]	26.4 (N= 10 R^2 0.78)	30.6 (N= 14 R^2 0.74)
Esters	167 (N= 29 R^2 0.828)	2975 (N= 19 R^2 0.992)	12.7 (N= 2 R^2 1.0)
Phenols	211 (N= 78 R^2 0.86)	39.6 (N= 48 R^2 0.6)	1715 (N= 7 R^2 0.91)

N = number of chemicals used to generate QSAR, R^2 = R^2 of QSAR (Clements 1996).

The lowest predicted endpoint is for green algae using the ester QSAR. It should be noted that this QSAR is based on a limited data set for which details of the chemicals used to generate the relationship are not available. Hence, the level of uncertainty in estimates based on this QSAR would be high. In addition, the toxicity effect due to the presence of the three functionalities within the molecule is uncertain, as most results are based on single functionality chemicals.

Similar modelling for the free acid (tyrosine) using the US EPA ECOSAR program predicts substantial reductions in the toxicity. These results are summarised below.

Functional Group	*End point*		
	Fish (LC50, mg/L)	*Daphnid (LC50, mg/L)*	*Green Algae (EC50, mg/L)*
Aliphatic Amines-acid	1.27×10^5	5780	2980
Phenols-acid	55100	3360	1.91×10^6

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical will be totally released into the environment with almost all expected to be

discharged into sewerage systems through washing off from the hair. It is expected that a small amount will remain in the consumer product containers and will be disposed of to landfill or recycled.

The notified chemical is highly soluble in water and thus will be mobile in both the aquatic and terrestrial compartment. It will readily hydrolyse in natural waters at environmental pH values. Under the basic conditions generally found in the sewer (pH 8) the notified chemical will be deprotonated and hydrolyse rapidly, to give the amino acid tyrosine, already present from natural sources. Residual chemical disposed of to landfill with empty containers are also expected to slowly adsorb to soil particles and be destroyed by similar mechanisms to those operating in sediments.

As the majority of the notified chemical in the haircare products will eventually be released into the aquatic environment via the sewerage systems the predicted environmental concentration (PEC) in the aquatic environment is estimated using a worst-case scenario (Environment Australia 2003). Australia has a population of approximately 20 million people, and an average value for water consumption of 200 L/person/day has been adopted for this national level assessment (4000×10^6 L/day for total population).

Based on annual imports of 1125 kg per annum, and assuming the majority of this is eventually released to sewer and not removed during sewage treatment processes, the daily release on a nationwide basis to receiving waters is estimated to be 3.1 kg/day. Therefore, the concentration of notified chemical in the Australian sewerage network may approximate 0.8 μg/L (ie 1125×10^6 mg ÷ 365 days/year ÷ 4000×10^6 L). Based on dilution factors of 1 and 10 for inland and ocean discharges of treated sewage treatment plant (STP) effluents, outfalls PECs of the notified chemical in freshwater and marine surface waters may approximate 0.8 μg/L and 0.08 μg/L, respectively.

The ready biodegradability test results showed that up to 99 % (based on DOC) of the notified chemical was eliminated after 28 days and therefore the notified chemical was considered to be readily biodegradable. The SIMPLETREAT model (European Commission 2003) for modelling partitioning and losses in STPs was used to estimate the proportions of the chemical partitioning into the different environmental compartments. The results indicate that when the notified chemical (1125 kg) is released into the aqueous phase of a STP, about 13% (146 kg) partitioned to water and 87% (979 kg) degraded while there is no release to air through volatilisation or partitioning to biosolids. These results are consistent with the expected low volatility, high solubility and low estimated log Pow values of the notified chemical.

Assuming 13% of the notified chemical (up to 146 kg) may potentially remain in solution, the following PECwater and PECsoil values were obtained (Environment Australia 2003). The worst-case scenario daily predicted environmental concentration (PEC) for the aquatic environment resulting from the nationwide release of the notified chemical into the sewage systems is reduced to 0.10 μg/L prior to any dilution. Based on dilution factors of 1 and 10 for inland and ocean discharges of treated STP effluents, outfalls PECs of the notified chemical in freshwater and marine surface waters may approximate 0.10 μg/L and 0.010 μg/L, respectively.

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 0.1 m of soil (density 1000 kg/m^3). Using these assumptions, irrigation with a concentration of 1.0×10^{-4} mg/L may potentially result in a soil concentration of approximately 1.0 ng/kg.

Bioaccumulation is not expected due to the high water solubility and estimated low log Pow of the notified chemical, which indicates a poor affinity to lipids. The readily biodegradable nature of the notified chemical would also limit its bioaccumulation potential.

9.1.2. Environment – effects assessment

The lowest predicted toxicity endpoint is for green algae based on the ester QSAR. Given the limited data set used to derive this endpoint and the absence of measured data an assessment safety factor of 1000 has been selected. The PNEC is calculated by taking the estimated LC50

value and dividing this value by an assessment safety factor. This would give a PNEC value of 12.7 µg/L.

9.1.3. Environment – risk characterisation

The estimated risk quotient values based on the scenario of discharging the entire imported notified chemical into sewage systems in Australia are less than 1. Treatment in STPs further reduces the risk as shown below. Therefore, the proposed use of the notified chemical is unlikely to pose an unacceptable risk to the aquatic life considering also that it will degrade to a naturally occurring amino acid already present in the sewer.

	Australia-wide STPs		
Location	*PEC*	*PNEC*	*Risk Quotient (RQ)*
Ocean outfall	0.08 µg/L (0.01 µg/L) #	12.7 µg/L	0.006 (0.0008)#
Inland river	0.8 µg/L (0.1 µg/L) #	12.7 µg/L	0.06 (0.008) #

PEC and RQ values calculated assuming 13% of the notified chemical partitioned into water and 87% degraded during the STP process based on SIMPLETREAT model.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

The notified chemical is introduced as a constituent of ready-to-use haircare products in consumer packages, occupational exposure would be limited to handling of spillages during an accident. The MSDS indicates collection and disposal of the spills will be in accordance with the official regulations. The good housekeeping practices and safe handling procedures will help further limit worker exposure to the notified chemical.

9.2.2. Public health – exposure assessment

Consumers of cosmetic gels, creams and lotions, possibly several hundred thousands, may be exposed to the notified chemical at levels of 0.014%. The total daily exposure of an individual is estimated to be 0.003 mg/kg bw or 0.16 mg (not adjusted for body weight) with dermal and ocular contact likely to be the main route of exposure. The dietary requirement for L-tyrosine is 14 mg/kg bw/day and the low therapeutic dose of L-dopa is 200 mg/day, the margin of exposure to the notified chemical relative to these levels is calculated to be 4667 (14 ÷ 0.003) and 1250 (200 ÷ 0.16) respectively. Hence, the public exposure is determined to be low.

9.2.3. Human health - effects assessment

The notified chemical at 0.1% was a slight skin irritant in a human patch test, but showed no evidence of sensitisation in subjects exposed to the same level. It is an eye irritant in vitro. Based on the available toxicity data of its analogues, the notified chemical would be expected to have low orders of single and repeat dose toxicity by oral and parenteral routes. However, its genotoxicity is uncertain because although the notified chemical was not mutagenic in a bacterial reverse mutation assay, its analogues are found clastogenic in vitro. The meaning of these results in practice is not clear as a positive result was found for the nutrient, tyrosine. The robust estimated Kp value of the analogue L-tyrosine methyl ester (CAS no. 1080-06-4) is in the range of 10^{-4} cm/h, which is indicative of relatively poor skin penetration potential. The hydrochloride salt of this material would be expected to be more water soluble than the methyl ester, and hence a similar or poorer skin permeant. Therefore, the notified chemical would not pose a significant health hazard when used in the proposed manner.

Based on the available data, the notified chemical is classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2002).

9.2.4. Occupational health and safety – risk characterisation

The OHS risk presented by the notified chemical is expected to be negligible, given the low probability of exposure, the good work practices and safety measures for handling cosmetic products including use of appropriate personal protective equipment by workers.

9.2.5. Public health – risk characterisation

A risk of eye irritancy on exposure to notified chemical is considered not significantly different from currently marketed benchmark haircare formulations. In addition, given the notified chemical will only be used at a low concentration of 0.014% in the end use products, together with its expected poor skin penetration potential, the risk to public health is determined to be low.

10. CONCLUSIONS – ASSESSMENT LEVEL OF CONCERN FOR THE ENVIRONMENT AND HUMANS

10.1. Hazard classification

Based on the available data the notified chemical is classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*. The classification and labelling details are:

R36 – Irritating to eyes.

As a comparison only, the classification of 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.

The notified chemical is classified as an eye irritant (category 2) under the GHS.

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio, the notified chemical is not considered to pose a risk to the environment based on its reported use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is Low Concern to occupational health and safety under the conditions of the occupational settings described.

10.3.2. Public health

There is No Significant Concern to public health when used in the proposed manner.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the product containing the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 2003). It is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

11.2. Label

The label for the product containing the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS

Hazard Classification and Labelling

- The NOHSC Chemicals Standards Sub-committee should consider the following health hazard classification for the notified chemical:
  - R36 – Irritating to eyes.

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - ≥ 20%: R36 (Obligatory) – Irritating to eyes.

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of finished products containing the notified chemical:
  - Adequate training for staff in safe handling procedures;

  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 NOHSC *Approved Criteria for Classifying Hazardous Substances*, 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/release of the notified chemical should be handled by containing, adsorbing with inert, damp, non-combustible material and flushing the area with flooding amounts of water.
- Do not contaminate drainage or waterways.
- Avoid direct discharge into drains.

12.1. Secondary notification

The Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act:
  - if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

No additional secondary notification conditions are stipulated.

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