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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

β-Alanine, N-(2-carboxyethyl)-N-dodecyl-, disodium salt, compd. with 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1- benzopyran-6-yl dihydrogen phosphate (1:1)

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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
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
ISP (Australasia) Pty Ltd (ABN 27 000 011 923)
73-75 Derby Street
SILVERWATER, New South Wales 2128

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: [*List]*
Composition information
Specific purity
Impurity information
Spectral data
Methods of detection & determination
Specific use
Identity of the finished product manufacturer/receipt
Manufacturing information

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Previously introduced under an exemption from notification under section 21(4) of the *Industrial Chemicals (Notification and Assessment) Act 1989*.

NOTIFICATION IN OTHER COUNTRIES
Canada Schedule 1 Notification in 2003.
EU VII A Notification in 2004.

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
β-Alanine, N-(2-carboxyethyl)-N-dodecyl-, disodium salt, compd. with 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1- benzopyran-6-yl dihydrogen phosphate (1:1)

OTHER NAME(S)
Disodium Lauriminodipropionate Tocopheryl Phosphate, Laurimino Dipropionic Acid Tocopheryl Phosphate

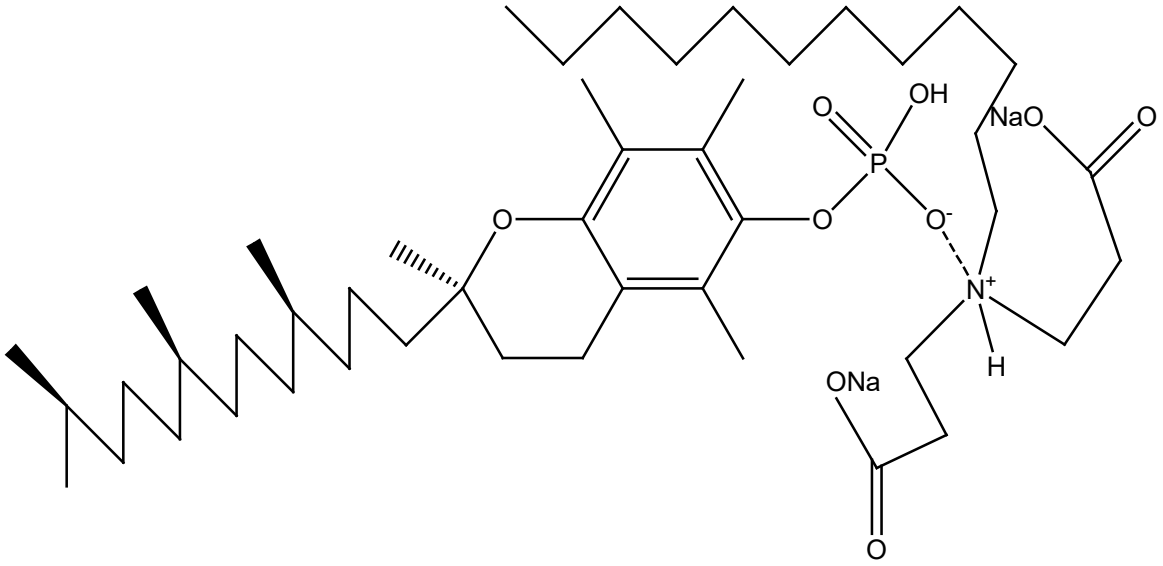
MARKETING NAME(S)
Vital ET
As a freeze-dried solid Vital ET contains over 50% Disodium Lauriminodipropionate Tocopheryl Phosphate, however, this product is marketed as a 40% aqueous solution.

CAS NUMBER
648891-82-1

MOLECULAR FORMULA

$C_{29}H_{51}O_5P.C_{18}H_{35}NO_4.2Na$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
884.14

METHODS OF DETECTION AND DETERMINATION

METHOD	UV, IR
Remarks	The notified chemical is a complex reaction product and there are no specific methods relating to its detection and determination. However, diagnostic spectral data are available and the notified chemical may be quantitatively determined by UV/VIS and IR spectrophotometry with absorbance detection at appropriate analytical wavelength.
TEST FACILITY	Covance Laboratories Ltd (2003)

3. COMPOSITION

DEGREE OF PURITY
> 50%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None.

ADDITIVES/ADJUVANTS
None.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical is not manufactured in Australia. It is imported into Australia as a 40% aqueous solution of the notified chemical.

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

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

USE

Skin conditioning agent for skin care products at up to 3%.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Melbourne, Victoria.

TRANSPORTATION AND PACKAGING
Vital ET containing > 50% Disodium Lauriminodipropionate Tocopheryl Phosphate is not manufactured in Australia, but imported as 40% aqueous solution.

The 40% Vital ET aqueous solution is transported into Australia by ship in 10 kg pails. The 40% Vital ET aqueous solution is transported from the dockside to the formulation site, where it is stored and formulated into skin care products.

The finished skin care product is packaged into consumer packaging (eg. Plastic tubes and bottles).

These bottled products are then shrink-wrapped and packed into cardboard cartons before being transported by road to various warehousing facilities around Australia for sale in supermarkets, pharmacies and health product stores.

5.2. Operation description

During the formulation of skin care products the solution of the notified chemical is dispensed directly into the mixing vessel manually. Other ingredients are added to make skin care formulations containing approximately 3% of the notified chemical, and the mixture stirred until well blended.

Samples of the finished product are tested by the Quality Assurance Laboratory before being filled into the consumer packaging (eg. Tubes and bottles), using automated lines.

The final packaged product is sold to consumers through supermarkets, pharmacies and health products stores.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Storage and transport			
Transporting from dock to manufacturer's site for reformulation (loading/unloading trucks) (sealed products only)	2	0 hours/day	5 days/year
Store person (sealed product only)	1	0 hours/day	10 days/year
Manufacture of skin care products			
Dispensing staff	2	0.25 hours/day	5 days/year
Plant operators (manufacturing)	2	4 hours/day	5 days/year
Line operators	6	4 hours/day	5 days/year
Quality control – chemical testing	2	0.25 hours/day	10 days/year

Exposure Details
Transport and storage
Transport and storage workers are not expected to be exposed to Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) as they are handling closed containers and Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) is supplied in 10 kg pails and transported in secure pallets. Exposure is possible in the event of an accident where the packaging is breached.

Formulation of skin care products

The batching and mixing areas are all equipped with high air change positive pressure air and exhausts. However, dermal and limited ocular exposure to 40% aqueous solution of Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) may occur when opening and closing the 10 kg pails and when adding the notified chemical manually into mixing vessel, and connecting and disconnecting transfer and filling lines. Inhalation exposure is not expected, as the notified chemical is in solution form and the processes are not expected to generate aerosols.

Dermal exposure to skin care product containing approximately 3% Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) may also occur due to drips and spills and if containers are overfilled at the filling station. Skin contamination may occur when maintenance workers are cleaning equipment and during maintenance of equipment. Workers involved in the above activities wear personal protective equipment such as, overalls, safety glasses, safety shoes, shoe covers, gloves, hair covering and facemasks.

Quality Control
During quality control there is a limited chance for dermal exposure to small quantities of the notified chemical at 40% or at up to 3% in the finished product during sampling. Quality Assurance personnel are required to wear personal protective equipment (lab coats, hair protection, eye protection and gloves) to minimise exposure to finished goods through splashes and spills.

Retail sale
Retail workers (eg. supermarkets, health product stores and pharmacies) unpack the boxes and place the consumer packaging (eg. 100 g, 200 g tubes or bottles) containing the notified chemical on store shelves. Exposure of retail workers is limited to spills from damaged containers.

5.4. Release

RELEASE OF CHEMICAL AT SITE
The notified chemical will not be manufactured in Australia, but imported as 40% Vital ET aqueous solution. Local operations will include transport and storage, formulation, filling and packaging of finished products containing the notified chemical. Release to the environment may occur in the unlikely event of an accident during transport or an accidental spill. The 10 kg pails of 40% aqueous solution of Vital ET will be transported directly to the Australian manufacturer (storage & formulation site) of skin care products for formulation of creams, lotions etc.

During the formulation of the skin care products it is estimated that up to 0.25 kg per annum of Vital ET will be released into the environment as a result of accidental spills and wash down of plant equipment. Empty pails are washed out and disposed of according to local regulations and industry standard operating practices. All rinsate go into a trade waste system where they are treated prior to release into the sewer.

RELEASE OF CHEMICAL FROM USE
The formulated skin care products would be packaged into consumer packaging, such as plastic jars and sold to retailers (and eventually consumers) in the consumer packaging and the residues they contain will be disposed of in domestic landfill. The residues in the containers are expected to account for approximately 4.5% of the import volume of the notified chemical. Practically all the notified chemical will enter the sewer during use of the consumer products when the wash water is released.

5.5. Disposal

Empty containers will be disposed to landfill via household garbage collection.

5.6. Public exposure

Skin care products containing up to 3% of the notified chemical will be sold to the general public. It is estimated that approximately 1-5g of the product will be used in each application and that the products are likely to be used daily.

Members of the public will therefore make dermal contact and possibly accidental ocular contact with product containing the notified chemical. However, exposure will be reduced by the low percentage of the notified chemical in consumer products (up to 3%).

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Freeze-dried buff solid powder (marketed as 40% by weight aqueous emulsion).

Melting Point/Freezing Point Melting endotherm observed for the solid: 218.5ºC.
Freezing point not determined.

METHOD OECD TG 102 Melting Point/Melting Range.
EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks A melting endotherm was observed, with a mean onset at 218.5°C and a mean peak at 221.7°C.
TEST FACILITY Covance Laboratories Ltd. (2004f)

Boiling Point None. Solid decomposes at temperature above 250ºC.

METHOD OECD TG 103 Boiling Point.
EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Boiling did not occur, but decomposition was observed starting at 250°C.
TEST FACILITY Covance Laboratories Ltd. (2004f)

Density 1156 kg/m^3 at 20.0ºC

METHOD OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks The relative density of the test material (solid) was determined to be 1.158 at 20.0°C by a gas comparison pyknometer method.
TEST FACILITY Covance Laboratories Ltd. (2004f)

Vapour Pressure Not determined.

METHOD OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Knudsen Effusion technique was used on the solid. The multi-component nature of the test substance led to very inconsistent results with erratic weight losses being measured. The data generated for the test substance did not permit vapour pressure to be determined. Due to the ionic nature of the notified chemical, vapour pressure is expected to be low.
TEST FACILITY Covance Laboratories Ltd. (2004f)

Water Solubility 16.97×10^{-3} g/L at 20ºC

METHOD OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks The Shake Flask Method was used on solid after a preliminary test was performed. Three pairs of closed flasks containing the notified chemical were stirred at 30°C for 24, 48 and 72 h respectively. They were then transferred to another bath at 20ºC and equilibrated for 24 h prior to analysis by HPLC.

TEST FACILITY Covance Laboratories Ltd. (2004f)

Hydrolysis as a Function of pH
METHOD OECD 111 and EC Directive 92/69/EEC Method C7

pH	*Temperatures (°C)*	*Half-life (days)*
4	50	8.6

	55	15.9
	69	31.0
7	50	5.4
	55	9.7
	69	4.0
9	50	10.4
	55	20.0
	69	9.5

Remarks The test substance is a tocopherol phosphate complex in which the individual components hydrolyse at different rates. The rate of hydrolysis was therefore not pseudo first order. It was not possible to plot the regression analysis to extrapolate the hydrolysis rates at 20ºC. Hydrolysis may be expected to be relatively slow at 25ºC.

TEST FACILITY Covance Laboratories Ltd. (2004g)

Partition Coefficient (n-octanol/water) Log Pow at 25°C = 1.09

METHOD EC Directive 92/69/EEC A.8 and OECD Test Guideline 117 - Partition Coefficient.

Remarks The partition coefficient was estimated by the HPLC simulation method using isocratic elution. It was possible to establish the calibration line with six different calibration compounds, four eluting before the test compound and two after. The test substance eluted as a single component exhibiting a retention time corresponding to a log Pow value of 1.09 (95% confidence limits 1.02 to 1.34).

TEST FACILITY Covance Laboratories Ltd. (2004f)

Adsorption/Desorption – screening test Log Koc = 1.27

METHOD OECD TG 121 and EC Directive 2001/59/EC Method C19

Remarks The Log Koc of the notified chemical was estimated by HPLC simulation procedure with 7 references using isocratic elution. The test substance eluted as a single component after the first two reference substances with a retention time equivalent to a log Koc value of 1.27 and within a 95% confidence range of 0.98 to 1.47.

TEST FACILITY Covance Laboratories Ltd. (2004g)

Dissociation Constant Solid does not exhibit salt like behaviour, but in solution is expected to remain ionized throughout the environmental pH range of 4-9.

METHOD Vapour pressure osmometry and Electrospray mass spectrometry

Remarks No evidence of ion separation in a high dielectric constant solvent.

TEST FACILITY Victoria University (2002)

Particle Size Test not conducted

Remarks The substance is marketed as 40% by weight aqueous emulsion

Flash Point Test not conducted

Remarks The notified chemical is marketed as 40% by weight aqueous emulsion, therefore flash point not applicable.

Flammability Limits Not highly flammable.

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks The moisture content of the test substance (solid) was determined under reduced pressure at room temperature to be 0.9%. The test substance ignited immediately, burned briefly and then extinguished, leaving a clear yellow viscous liquid residue, and is not classified as highly flammable.
TEST FACILITY Covance Laboratories Ltd. (2003)

Autoignition Temperature > 430ºC (solid)

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks No relative self-ignition (auto-flammability) was observed below 430°C.
TEST FACILITY Covance Laboratories Ltd. (2004)

Explosive Properties No potential for explosion is likely to be present (solid).

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks The oxygen balances for both of the main components are outside the region where a potential for explosion exists. There are no potential auxoploses/plosophores (aromatic nitro group) present. The enthalpies of the exotherma are significantly smaller than the trigger value. It is therefore concluded that no potential for explosion is likely to be present.
TEST FACILITY Covance Laboratories Ltd. (2004)

Reactivity

Remarks The notified chemical is expected to be stable under normal environmental conditions. No test of oxidising properties was performed. The notified chemical does not have any structural indications of oxidising properties or other unusual activity.

Surface Tension 67.8 mN/m

METHOD EC Directive 92/69/EEC A.5 and OECD Guideline 115 - Surface Tension.

Remarks The surface tension at 20ºC of the notified chemical was determined at 90% of water saturation concentration by a surface tension balance. The test material is considered not to be a surface-active material.

TEST FACILITY Covance Laboratories Ltd. (2004f)

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 > 2000 mg/kg bw	low toxicity
Rat, acute dermal LD50 > 2000 mg/kg bw	low toxicity
Rat, acute inhalation	Not available
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	non-irritating
Guinea pig, skin sensitisation	Limited evidence of sensitisation potential
Mouse, skin sensitisation – local lymph node assay	Not sensiting
Human, repeat insult patch test	No dermal irritation/No allergic contact sensitisation
Rat, oral repeat dose toxicity – 28 days.	NOAEL> 1000 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration test	non genotoxic
Human, Phototoxicity	Non-phototoxic
Human, Photoallergenicity	Non-photoallergenic

7.1. Acute toxicity – oral

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD
- Species/Strain: Rat/Wistar albino rats
- Vehicle: Distilled water
- Remarks - Method: Five male and five female Wistar albino rats were dosed orally with Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) at 2000mg/kg of body weight.
The rats were observed 1, 2 and 4 hours post-dose and once daily for 14 days for toxicity and pharmacological effects. The animals were observed twice daily for mortality. Body weights were recorded immediately pretest, weekly and at termination in the survivors. All animals were examined for gross pathology.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
Treatment	5/sex	2000	0/10

- LD50: > 2000 mg/kg bw
- Signs of Toxicity: Soiling of the anogenital area and localised alopecia were observed in some animals during the study.
- Effects in Organs: None. Necropsy results were normal.
- Remarks - Results: All animals survived during the study period. One female lost weight during the second week of the observation period. At necropsy, localised alopecia was noted in the front limbs of 4/10 animals. This is attributed to the design of the feeders rather than to any effect of the test material.

CONCLUSION: The notified chemical is of low toxicity via the oral route.

TEST FACILITY: MB Research Laboratories (2003)

7.2. Acute toxicity – dermal

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD	OECD TG 402 Acute Dermal Toxicity.
Species/Strain	Rat/ New Zealand white rabbits
Vehicle	Distilled water
Type of dressing	Semi-occlusive.
Remarks - Method	Five male and five female New Zealand white rabbits received a single dermal application of Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) at 2000 mg/kg bodyweight. The test substance was kept in contact with the skin for 24 hours. Dermal responses were recorded at 24 hours post-dose and on days 7 and 14. All animals were observed for signs of toxicity and pharmacological effects 1, 2 and 4 hours post-treatment and then once daily for 14 days. Animals were observed twice daily for mortality. Body weights were recorded pretest, weekly and at termination in the survivors. All animals were examined for gross pathology.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
Treatment	5/sex	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	None. Very slight to well defined erythema and very slight to slight edema were observed at 24 hour observation period. Dermal effects were resolved by Day 7.
Signs of Toxicity - Systemic	None.
Effects in Organs	None. At necropsy, no abnormalities were found in any animal.
Remarks - Results	All animals survived the 2000 mg/kg limit dose. Two animals had diarrhea on post-treatment day 1. Body weight changes were normal in 9/10 animals. One animal lost weight during the second week of the observation period. However there was no net weight loss during the study period for this animal and its weight was within the normal range.

CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	MB Research Laboratories (2003a)

7.3. Acute toxicity – inhalation

There was no acute inhalation toxicity test submitted.

7.4. Irritation – skin

TEST SUBSTANCE	Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) on ACO-5031
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White rabbits
Number of Animals	3 (1 male, 2 females)
Vehicle	Distilled water
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	One male and two female New Zealand white rabbits each received a single dermal application of Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) (0.5 g) on one intact site per rabbit. The test sites were occluded for 4 hours and dermal reactions were scored at 60 minutes following patch removal. Reactions were scored again at

24, 48 and 72 hours. The skin was also evaluated for ulceration and necrosis or any evidence of tissue destruction at these time periods. Body weights were recorded pretest and at termination.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	0	1	60 minutes	0
Oedema	0	0	0	0	0	0

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

Remarks - Results: One animal had barely perceptible erythema, which persisted for 60 minutes following patch removal. Edema was absent at all observation time periods. All body weight changes were normal.

CONCLUSION: The notified chemical is non-irritating to the skin.

TEST FACILITY: MB Research Laboratories (2003b)

7.5. Irritation – eye

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD: OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain: Rabbit/New Zealand White rabbits
Number of Animals: 3
Observation Period: 72 hours
Remarks - Method: Initially, one animal was dosed with a syringe-type applicator since the test material formed a large clump upon dosing. The test material was administered on weight paper during the study.
One male and 2 female New Zealand white rabbits, received a single application of Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) (0.1 mL equivalent to 84mg) into the conjunctival sac of one eye of each rabbit.
The contra lateral eye, remaining untreated, served as a control. The eyes were examined and scored for effects on the cornea, iris and conjunctiva at 1, 24, 48 and 72 hours post-dose. Body weights were recorded pretest.
Sodium fluorescein dye procedures were used at the 24 hour observation interval. Ocular reactions were graded according to the numerical Draize technique.

RESULTS: All score for cornea, iris and conjunctiva effects were zero.

Remarks - Results: All eyes appeared normal at each observation period. There were no abnormal physical signs noted during the observation period.

CONCLUSION: The notified chemical is non-irritating to the eye.

TEST FACILITY: MB Research Laboratories (2003c)

7.6.1 Skin sensitisation- Guinea Pig Maximisation test

TEST SUBSTANCE: 30% Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) in water

METHOD: OECD TG 406 Skin Sensitisation - Guinea Pig Maximisation.
Species/Strain: Guinea pig/ Hartley Albino

PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 10% of test material in distilled water topical: 25% of test material in distilled water
MAIN STUDY	
Number of Animals	Test Group: 10 /sex Control Group: 5 / sex
INDUCTION PHASE	Intradermal injection Site a: 50% Freund's Complete Adjuvant (FCA) in distilled water Site b: 10% test substance in distilled water Site c: 50:50 FCA and 10% test substance Topical application 100% test substance The same induction procedures were carried out on control group (5/sex), except that the test material was replaced by distilled water in all doses.
Signs of Irritation	Intradermal Injections: the intradermal injections with FCA (with and without the test substance) caused discrete to moderate erythema – similar degree of erythema was observed on the sites treated with the test substance in distilled water. Intradermal injections of the vehicle alone did not exhibit any signs of irritation. Topical induction: 48 hours after removal of application at Day 14, discrete to moderate erythema was observed at the majority of sites treated with 100% test substance. The administration of vehicle alone exhibited discrete erythema in 2 animals.
CHALLENGE PHASE	Two weeks following the topical application, all animals were challenged by occluded application of the test material in distilled water to one flank and distilled water (vehicle) to the opposite flank. Test sites were assessed approximately 24 and 48 hours after patch removal.
Remarks - Method	No significant protocol deviation.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge*	
		24 h	*48 h*
Test Group	25%	1/20	0/20
Control Group	100% water	0/10	0/10

Remarks - Results	One animal in the test group had discrete erythema at 24 hour observation period. Soiling of the anogenital area was observed in both the test group and the vehicle control group and diarrhea was noted in the vehicle control group only.
CONCLUSION	There was limited evidence of skin sensitisation to the notified chemical under the conditions of the test ie. a weak sensitizing potential.
TEST FACILITY	MB Research Laboratories (2002)

7.6.2. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)
METHOD	OECD 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/ CBA/J
Vehicle	Reverse Osmosis (RO) Water
Remarks - Method	Dose levels for the study were based on a prestudy assessment of the solubility of the test substance in water & feasibility of dosing a suspension that indicated the maximum concentration was 28% w/v.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	67.8	1.0
5%	53.6	0.8
10%	48.6	0.7
25%	120.0	1.8
*Positive Control**		
25%	1104.2	19.2

*Hexylcinnamaldehyde in 4:1 (v/v) acetone/olive oil

Remarks - Results: All animals survived to the scheduled euthanasia. No signs of toxicity were observed. Three animals from the 25% test material group exhibited alopecia, and one of the same group had a scab/sore on the right ear. No significant changes in mean body weight were observed for treated groups compared with the naïve group & acetone/olive oil group.

The mean dpm values for animals treated with 25% Hexylcinnamaldehyde was statistically significant when compared with the group treated with acetone/olive oil.

CONCLUSION: There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY: Covance Laboratories Ltd. (2004c)

7.6.3 Repeated Insult Patch Test – human volunteers

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD: The test was conducted in accordance with ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56.

Study Group: 115 male and female subjects, ranging from 16-71 years completed the study.

Vehicle: Water

Study Design: Patches were applied 3 times per week, for 24 hours before removal, for a total of 9 applications.

Induction Procedure: Patch Test was conducted using 115 human subjects. Prior to study initiation, the test material was diluted to 5%.

Rest Period: Approximately 2 weeks after final induction.

Challenge Procedure: Following a 2-week rest period, challenge patches were applied to a virgin site on the back and allowed to remain in skin contact for 24 hours. Challenge sites were scored for erythema and edema 24 and 72 hours after application.

Remarks - Method: Each of subjects received the test material on the upper back area using semi-occlusive patch. Following a 24-hour exposure period, test patches were removed and sites scored for erythema and edema.

Fourteen of the starting 115 test subjects discontinued their participation in the study for various reasons unrelated to the testing material, therefore the results are based on the 101 subjects who completed the study.

RESULTS

Remarks - Results: No dermal reactions were exhibited during either the induction phase or challenge phase of the study.

CONCLUSION: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

diluted with water to 5% under semi-occlusive dressing did not indicate a potential for dermal irritation or allergic contact sensitisation under the conditions of the test.

TEST FACILITY Consumer Product Testing Co. (2002b)

7.7. Repeat dose toxicity

TEST SUBSTANCE Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) suspended in distilled water.

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.

Species/Strain Rat/Wistar

Route of Administration Oral – gavage

Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week

Vehicle Distilled water

Remarks - Method A minor amendment to study protocol was submitted. However, the protocol amendment did not alter the final results of the study.

The animals were observed once daily for signs of toxicity and pharmacological effects and twice daily for morbidity and mortality. Body weights were recorded pretest, weekly, at death and at study termination. Food consumption was calculated weekly. A Functional Observation Battery (FOB), designed to assess specific neurotoxicity and behavioral changes, was conducted on Days 23 and 29. Clinical chemistry, hematology and pathology evaluations were conducted. All animals were sampled on Day 29.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5 /sex	0	0
II (high dose)	5 /sex	1000	1/10
III (mid dose)	5 /sex	500	1/10
IV (low dose)	5 /sex	100	0

Mortality and Time to Death

1 female in Group II died on day 13, and 1 female in Group III died on day 15. Both deaths were attributed to gavage accidents and not due to the test material.

Clinical Observations

Clinical effects including lethargy, piloerection, tachypnea, wetness of the anogenital area, emaciation, few feces, yellow attaining of the anogential area, dyspnea, hunched posture, sluggish & cold to touch were reported in 2 animals in Groups II and III.

There were no significant differences between control and dosed groups in mean body weights (although isolated instances of weight loss were noted in individual animals), mean food consumption and FOB parameters.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were no significant differences between control and dosed groups in haematology parameters.

Mean SGPT enzymes levels of males In Group II were significantly greater than controls. In females, in Groups II & III mean potassium levels were significantly less than controls. Also in females, in Groups III & IV mean sodium levels were both significantly greater than controls.

Effects in Organs

The mean liver/body weight ratio in female control animals (2.82%) was significantly less than the mean liver/body weight ratio of the females in Groups II (3.13%).

Necropsy results in survivors were generally normal in all groups. Microscopic evaluations revealed no treatment related changes in male or female in Groups II and III. Microscopic changes observed in the lung of animals in groups II and III were likely the result of aspiration during gavage not considered to be treatment related. Other microscopic changes observed in various organs and tissue which occurred spontaneously were not considered to be treatment related.

Remarks – Results
The clinical effects observed in Groups II and III were not significant and animals appeared normal at the end of study period.

Necropsy results in survivors were generally normal in all groups. The significant differences noted in liver/body weight ratios, sodium & potassium levels in females & SGPT levels in male in treated groups compared with control group were not considered to be treatment related since microscopic evaluations revealed no changes in treated groups.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as >1000mg/kg bw/day in this study, based on the results.

TEST FACILITY MB Research Laboratories (2004)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure/Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Mammalian liver post-mitochondrial function (S-9) from rats pretreated with Aroclor 1254
Concentration Range in Main Test	Experiment 1 a) With metabolic activation: 1.6-5000 µg/plate. b) Without metabolic activation: 1.6-5000 µg/plate. Experiment 2 a) With metabolic activation: 156.25-5000 µg/plate. b) Without metabolic activation: 156.25-5000 µg/plate.
Vehicle	Water
Remarks - Method	A range-finding study was carried out in strain TA100 only, in absence and presence of S-9, using concentrations of test substance at 1.6, 8, 40, 200, 1000 and 5000 µg/plate, plus solvent and positive controls. No evidence of toxicity was observed following any of these treatments. All treatments in the presence of S9 were modified by the inclusion of a pre-incubation step.

RESULTS

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

Remarks - Results No substantial increase in the number of revertant colonies was seen in

any strain either in the presence or absence of metabolic activation.
All negative control data were within acceptable ranges. The mean number of revertant colonies on positive control treatments was significantly elevated.

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

TEST FACILITY: Covance Laboratories Ltd. (2004a)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD: OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Cell Type/Cell Line	Chinese hamster ovary (CHO)
Metabolic Activation System	Mammalian liver post-mitochondrial function (S-9) from rats pretreated with Aroclor 1254
Vehicle	1% carboxy methyl cellulose (1% CMC)
Remarks - Method	Preliminary solubility trial indicated that a suspension with 1% CMC at a dosable concentration of at least 210 mg/mL could be obtained. However in experiment 1, test substance at a concentration of 2100 µg/mL was too viscous to pipette therefore the highest concentration tested was reduced to 1000 µg/mL. Experiment 2 was repeated because it was not possible to select a suitable top dose for analysis following 3-hour treatment in the presence of S-9 since the required 50% cytotoxicity was not achieved and no precipitate was observed at the end of treatment incubation. In Experiment 1, the highest concentration analysed, 72.16 µg/mL in the absence of S-9 and 57.72 µg/mL in the presence of S-9, induced approximately 50% and 48% reduction in cell number respectively. In Experiment 2, the highest concentrations analysed, 120 µg/mL (-S9) and 67.11 µg/mL (+S9) induced approximately 40% and 57% reduction in cell number respectively. The highest dose level used (120 µg/mL) selected in the absence of S-9 was in excess of the solubility limit in culture medium.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Present			
Test 1	23.64*, 29.55, 36.94, 46.18*, 57.72*, 72.16, 90.19, 112.7, 140.9, 176.2, 220.2, 275.3, 344.1, 430.1, 537.6, 672.0, 840.0, 1050.0	3 hr	20 hr
Test 2	11.26, 14.07, 17.59, 21.99, 27.49*, 34.36*, 42.95, 53.69, 67.11*, 83.89, 104.9, 131.1, 163.8, 204.8, 256.0, 320.0, 400.0, 500.0	3 hr	20 hr
Absent			
Test 1	23.64, 29.55, 36.94, 46.18*, 57.73*, 72.16*, 90.19, 112.7, 140.9, 176.2, 220.2, 275.3, 344.1, 430.1, 537.6, 672.0, 840.0, 1050.0	3 hr	20 hr
Test 2	2.702, 3.378, 4.222, 5.278, 6.597*, 8.246, 10.31, 12.88, 16.11, 20.13, 25.17, 31.46*, 39.32, 49.15, 61.44, 76.80, 96.00, 120.0*, 150.0	20 hr continuous exposure	

*Cultures selected for metaphase analysis.

RESULTS

Metabolic	*Test Substance Concentration (µg/mL) Resulting in:*

Activation	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present			
Test 1	> 57.72	≥ 46.18	negative
Test 2	> 67.11	≥ 500	negative
Absent			
Test 1	> 72.16	≥ 176.2	negative
Test 2	> 120.0	≥ 39.32	negative

Remarks - Results	Treatment of cultures with the test substance in the absence and presence of S9 (both experiments) resulted in frequencies of cells with chromosome aberrations that were similar to concurrent vehicle control cultures. The numbers of aberrant cells (excluding gaps) in treated cultures fell within historical vehicle control range except at the intermediate concentration (34.36 µg/mL) analysed in the presence of S-9 in experiment2 where the frequency of cells with structural aberrations exceeded the normal range which was observed in a single range. This increase was not observed in the replicate culture at this concentration or in any other test substance treated cultures. It was of no biological significance. Sporadic increases in endoreduplicated cells were also observed following treatment in the presence of S-9 (both experiments). However, these increases were not significant and fell within the historical control range.
CONCLUSION	The notified chemical was not clastogenic to CHO treated in vitro under the conditions of the test.
TEST FACILITY	Covance Laboratories Ltd. (2004b)

7.10. Genotoxicity – in vivo

There was no genotoxicity – in vivo test submitted.

ADDITIONAL INVESTIGATIONS

7.11Ta. Phototoxicity – human volunteers

TEST SUBSTANCE	Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)
METHOD	
Study Group	10 male and female subjects, 18-65 years, fair skinned with skin types ranging from Types I – IV
Vehicle	Water
Remarks - Method	The test material was diluted to 5% and was applied to two test sites on the back of each subject (one site to be irradiated and the other site not to be irradiated). A third site was also selected as the control. Following a 24-hour exposure period under some occlusive dressing, the patches were removed. Both treated and control sites were examined at 24 and 48 hours following irradiation and scored for dermal reaction.
RESULTS	
Remarks - Results	No visible skin reactions were observed throughout the study. One of the test subjects discontinued the study for reasons unrelated to the testing material, therefore the results are based on nine (9) subjects.
CONCLUSION	Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) diluted with water to 5% under semi-occlusive dressing did not induce a response indicative of a phototoxic reaction.
TEST FACILITY	Consumer Product Testing Co. (2002)

7.11Tb. Photoallergy – human volunteers

TEST SUBSTANCE	Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)
METHOD	The test was conducted in accordance with ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56.
Study Group	28 male and female subjects, 18-65 years, fair skinned with skin types ranging Types I – III.
Vehicle	Water
Induction Procedure	The test material was applied to two test sites on the back of each subject (one site to be irradiated and the other site not to be irradiated). One to two applications per week, for a 3 to 4 week period, for a total of 6 inductions. Following a 24-hour exposure period under semi-occlusive patches, the patches were removed. One of the treated sites was irradiated with twice the subject's pre-determined minimal erythemal dose (MED). Test and control sites were examined 24 hours following irradiation of the test sites and graded for dermal response.
Rest Period	Approximately 2 weeks
Challenge Procedure	Following a two-week rest period, identical patches were applied to two sites previously unexposed to the test material. Twenty-four hours later the patches were removed. One of the treated sites and a non-treated control site were irradiated with a non-erythemogenic dose of UVA for 3 minutes. All challenge sites were evaluated at 24, 48 and 72 hours following irradiation.
Remarks - Method	The test material was diluted to 5% in water.
RESULTS	
Remarks - Results	Two of the test subjects discontinued the study for reasons unrelated to the testing material, therefore the results are based on 26 subjects.

CONCLUSION	Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) diluted with water 5% under semi-occlusive dressing did not induce a response indicative of a photoallergic reaction under the conditions of the test.
TEST FACILITY	Consumer Product Testing Co. (2002a)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
EC Directive 92/69/EEC C.4-C Biodegradation: Determination of the Ready Biodegradability: Carbon Dioxide Evolution Test.

Inoculum	Activated sludge from a sewage treatment works with a predominantly domestic catchment
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Titration
Remarks - Method	The test substance was suspended in a buffered mineral salts medium at a nominal concentration of 15 mg C/L. The medium was inoculated with micro-organisms derived from the activated sludge. Test vessels were incubated in darkness for 28 days. Four treatment groups were established in the system: a control consisting of inoculated mineral salts medium; a reference sodium benzoate at 15 mg C/L was used; the test substance was prepared at concentration of 15 mg C/L and a toxicity control was used to assess the biodegradability of the reference in the presence of the test substance.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
3	1	3	34
9	6	9	58
13	10	13	65
20	19	20	75
24	23	24	78
28	28	28	81

Remarks - Results: Mean carbon dioxide evolution from the notified chemical reached 10% of the theoretical maximum at the applied concentration on Day 13, and was 28% on Day 28. The test substance did not achieve 60% biodegradation within 10 days of 10% biodegradation being observed. The reference substance sodium benzoate achieved a 81% degradation on day 28 thus the validity of the test was met. The temperature and pH were within acceptable limits during the course of exposure.

CONCLUSION: The notified chemical is considered not readily biodegradable.

TEST FACILITY: Covance Laboratories Ltd. (2004d)

8.1.2. Bioaccumulation

No study was provided. However, based on the log Pow of 1.09, the notified chemical is unlikely to bioaccumulate.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl

Phosphate)

METHOD: OECD TG 203 Fish, Acute Toxicity Test – Rainbow Trout *(Oncorhynchus mykiss)* Under Static-Renewal Conditions.

Species	Rainbow trout *(Oncorhynchus mykiss)*
Exposure Period	96 h
Auxiliary Solvent	None
Water Hardness	40-44 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	The acute toxicity of the notified chemical to rainbow trout (*Oncorhynchus mykiss*) was determined in a 96-hour test with renewal of test media after 48 h. Following a settling period, the stirred and sonicated stock solution was observed to be slightly cloudy with undissolved test substance on the bottom of the tank and on the surface of the solution. The soluble fraction of the solution was siphoned from the aquarium. Nominal test concentrations at 0 and 48 h were prepared from the soluble portion. Aquaria were filled with 15 L of the test solution. Solutions prepared at 0 and 48 h were observed to be cloudy with undissolved material for the 0 h solution. Ten fish per treatment level and the control were tested, with two fish per exposure vessel.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0	0
1.3	0.66	10	0	0	0	0	0
2.5	1.0	10	0	0	0	0	0
5.0	2.3	10	0	0	0	0	0
10.0	4.4	10	0	0	0	0	0
20.0	11	10	0	0	0	0	0

LC50	> 11 mg/L at 96 hours.
NOEC (or LOEC)	11 mg/L at 96 hours.
Remarks – Results	No concentration tested resulted in 50% (or higher) mortality. The highest concentration producing 0% mortality was 11 mg/L and the lowest concentration producing 100% mortality was > 11 mg/L. Therefore, the 96-hour LC50 was empirically estimated to be > 11 mg/L. The measured concentrations represented the sum of tocopherol phosphate, tocopherol and ditocopherol phosphate. The mean recovery was 94.9% with a standard deviation of 8.5% and LOQ of 1.26 µg/L. Water quality parameters (pH, dissolved oxygen concentration and temperature) were within acceptable limits during the course of exposure.

CONCLUSION: The notified chemical is considered not toxic to fish up to its limit of solubility (11 mg/L in this instance).

TEST FACILITY: Springborn Smithers (2004a)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE: Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD: OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – under static-renewal conditions

Species	*Daphnia magna*
Exposure Period	48 h
Auxiliary Solvent	None

Water Hardness	170-180 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	The acute toxicity of the notified chemical to *Daphnia magna* was determined in a 48-hour static test without renewal of test media. The test solution was prepared by mixing the test substance and dilution water at 20 mg/Lwith stirring for approximately for 4 h. Following the stirring, the solution was observed to be cloudy and white in colour with no visible undissolved test substance present. The solution was allowed to settle and the soluble portion was removed through the sidewall drain in the bottle. Nominal test concentrations were prepared from the soluble portion. The number of immobilised daphnids was recorded at 24 and 48 h of exposure. Biological observations and observation of the physical characteristics of each test solution were also recorded at 0, 24 and 48 h. The pH, dissolved oxygen concentration and temperature were measured at 0, 24 and 48 h at each treatment level and the control.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
1.3	0.48	20	0	0
2.5	0.62	20	0	0
5.0	1.4	20	0	0
10.0	2.1	20	0	0
20.0	4.5	20	0	1

EC50	> 4.5 mg/L at 48 hours
NOEC	2.1 mg/L at 48 hours
Remarks - Results	Following 48 hours of exposure, immobilization of 5% was observed among daphnids exposed to the 4.5 mg/L treatment level. Several surviving daphnids exposed to this treatment level were observed to be light and pale in colour while two daphnids were observed to be swimming carrying particulate matter. No immobilization or sublethal effects were observed among daphnids exposed to the remaining treatment levels tested (0.48, 0.62 and 1.4 mg/L) or the control. Analysis of the control samples resulted in measured concentrations which are consistent with the recovery range of 71.0-91.8%. The water quality parameters (pH, temperature and dissolved oxygen concentrations) were found to be within the acceptable limits. All solutions were clear and colourless except at 20 mg/L where it was cloudy and white in colour.

CONCLUSION The notified chemical is considered to be not toxic to daphnia up to its limit of water solubility (4.5 mg/L).

TEST FACILITY Springborn Smithers (2004b)

8.2.3. Algal growth inhibition test

TEST SUBSTANCE Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)

METHOD OECD TG 201 Alga, Growth Inhibition Test.

Species	Freshwater Green Alga *(Pseudokirchneriella subcapitata)*
Exposure Period	… hours
Concentration Range	Nominal: 0.049, 0.16, 0.54, 1.8 and 6.0 mg/L Actual: 0.014, 0.043, 0.20, 0.49, 1.8 and 6.4 mg/L

Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	None
Remarks - Method	Based on the results of the preliminary test, nominal concentrations were used for the definitive test. The inhibition of the growth and growth rate in relation to the control was determined after 72 h of incubation. Three replicate flasks were established for each treatment and control. Measurement of conductivity and pH in each test concentration were recorded at the start and finish of the test. Algal densities in each test vessel were monitored at 24, 28 and 72 h after the start of the test. Visual observations were made on the cell size, shape, colour, occurrence of flocculation and adherence to glass walls.

RESULTS

Biomass		*Growth*	
EbC50	*NOEC*	*ErC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
1.9	0.49	4.7	0.49
(CI: 1.5 – 2.8)		(CI: 4.3 – 5.2)	

Remarks - Results	The results are based on mean measured concentrations represented by the sum of measured tocopherol phosphate, tocopherol and ditocopherol phosphate concentrations. Statistical analysis determined a significant difference in total biomass in the 1.8 and 6.4 mg/L treatment levels when compared to the total biomass in the control. Based on these results, the NOEC for total biomass was determined to be 0.49 mg/L. The analysis also determined a significant reduction in average growth rate in the 1.8 and 6.4 mg/L treatment levels when compared to the total biomass in the control. The NOEC for average growth rate was also determined to be 0.49 mg/L. The temperature, pH and conductivity were within acceptable limits during the course of the exposure.
CONCLUSION	The notified chemical is considered to be toxic to alga.
TEST FACILITY	Sprinborn Smithers (2004c)

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate)
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 87/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sludge
Exposure Period	3 h hours
Concentration Range	Nominal: 1, 10, 100 and 1000 mg/L
Remarks – Method	Samples of activated sludge were exposed to the notified chemical at nominal concentrations ranging from 1.0 to 1000 mg/L and their respiration rates measured after 3 h contact time. The reference inhibitor 3,5-dichlorophenol was run at concentrations of 5, 15 and 45 mg/L.
RESULTS	
IC50	> 1000 mg/L
NOEC	1000 mg/L
Remarks – Results	The test substance did not inhibit the respiration rate of activated sludge at concentrations up to and including 1000 mg/L. Consequently, the 3 h EC50 could not be calculated but it is determined to be > 1000 mg/L. The

	EC50 estimate of 14.7 mg/L for the reference is within the acceptable range thus validating the test.
CONCLUSION	The notified chemical is considered not to be inhibitory to sewage micro-organisms.
TEST FACILITY	Covance Laboratories Ltd. (2004e)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical is to be used in skin care formulation and is moderately soluble in water. It is considered not readily biodegradable (28% biodegradable after 28 days in a closed bottle test). The notified chemical is a tocopherol phosphate complex in which the individual components hydrolyse at different rates with half-life ranging from 4-30 days at pH 4, 7 and 9. It has a log Pow of 1.09 and a log Koc of 1.27 indicating that it is likely to associate with the aqueous phase following its use as skin care products. It is anticipated that prolonged residence in an active landfill will eventually degrade the notified chemical disposed of directly through normal garbage.

Assuming a worst-case scenario that all of the notified chemical is eventually released to sewer, a calculated worst-case scenario daily PEC in the sewer effluent is 2.1 µg/L In calculating the PEC, the following were assumed: (1) usage of the maximum import volume of 3 tonnes is evenly distributed over a 365 day period; (2) usage is nationwide, with a population of 20 million contributing 200 L of water per person per day to the sewer, (3) there is no adsorption or degradation in the sewer prior to release.

Based on the respective dilution factors of 1 and 10 for rural areas and coastal discharges of effluents, the PECs of the notified chemical in rural areas and coastal water may approximate 2.1 and 0.21 µg/L, respectively.

SIMPLETREAT modelling is not possible due to the lack of a vapour pressure result. However, the logKoc of 1.27 suggests the majority will be retained in the water column.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 4.08 mg/kg (dry wt), assuming 20% attenuation in sludge during the STP process. This is based on the assumption that 0.1 tonne of biosolids is generated for each ML of STP effluent and the consumption of 4000 ML/day for total population per year (20% X 3 tonnes/4000 X 0.1 X 365 = 4.08 mg/kg). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1000 kg/m^3 and a soil mixing zone of 0.1 m, the concentration of the notified chemical may approximate 0.408 mg/kg in the applied soil, assuming accumulation of the notified chemical in soil for 10 years under repeated biosolids application.

The effluent re-use (eg. irrigation purposes) concentration of the notified chemical may potentially approximate 1.68 µg/L, assuming 80% remains in solution during the STP process. STP effluent re-use for irrigation in Australia 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 1.68 µg/L may potentially result in a soil concentration of approximately 168 µg/kg assuming accumulation of the notified chemical in soil for 10 years under repeated irrigation.

The worst-case PECs values are summarised below:

Sewage effluent/coastal city = 0.21 µg/L
Sewage effluent/rural areas = 2.1 µg/L.
Soil concentrations after 10 years application of biosolids = 0.408 mg/kg
Soil concentrations following 10 years irrigation with effluent = 168 µg/kg.

In the case of landfill, the notified chemical is likely to be slowly degraded by biotic and abiotic processes. Based on the notified chemical's $logP_{o/w}$ of 1.09, the substance is not expected to bioaccumulate.

9.1.2. Environment – effects assessment

The most sensitive species was algae with 72 h LC50 of 1.9 mg/L. A predicted no effect concentration (PNEC) of 19 µg/L has been derived by dividing the end point of 1.9 mg/L by a safety factor of 100 as data for 3 trophic levels are available.

9.1.3. Environment – risk characterisation

Location	PEC (µg/L)	PNEC (µg/L)	Risk Quotient (RQ)
Australia-wide STPs (worst case)			
Ocean outfall	0.21	19	0.01
Inland river	2.1	19	0.1

The risk quotients indicate an acceptable risk for both marine and freshwater organisms. This is without taking movement to sludge into account, which is expected to remove some chemical from the water column.

Given the low volume usage and the disperse use, the notified chemical is unlikely to pose an environmental risk under the proposed use pattern.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Formulation

Dermal and possibly ocular exposure to the notified chemical could occur during the transfer of the fragrance mixture to the blending vessel. The level of exposure would vary from site to site depending on the level of automation of the formulation process. The estimated dermal exposure is 210 mg/day, based on EASE model using reasonable worst case defaults for the exposure scenario 'manual addition of liquids' (European Commission, 2003) and assuming the notified chemical is present at concentration of 50%. Therefore, for a 70 kg worker and a 100% dermal absorption factor, systemic exposure is estimated to be 3 mg/kg bw/day.

Exposure would be further limited by the use of PPE.

Following formulation of the end use products, exposure to the notified chemical is expected to be very low due to the low concentration of the notified chemical (< 3%) and the expected use of PPE.

End use

Workers may be exposed to the notified chemical during final application of the formulated cleaning/cosmetic products or during their addition to water if dilution is required. Although the level and route of exposure will vary depending on the method of application and work practices employed, exposure is considered to be low due to the low concentration of the notified chemical (3%).

9.2.2. Public health – exposure assessment

Since the notified chemical will be in products sold to the general public, widespread public exposure to the notified chemical at a concentration up to 3% is expected. Based on exposure to a range of household, personal care and cosmetic products in Europe (SDA, 2005), public exposure (dermal and inhalation) to the notified chemical through use of a wide range of products containing the notified chemical, is estimated to be 7.9 mg/kg bw/day, assuming a bodyweight of 60kg, a 100% dermal absorption factor, a concentration of 3% and that product usage (amount used per use and frequency of use) is similar in Australia to Europe. This estimate is considered to be an overestimate as it assumes all products (household, personal care and cosmetic) used by one person contain the notified chemical and uses the maximum 'product amount used' from the range in the dataset.

Based on exposure to a range of household, personal care and cosmetic products in Europe (SDA, 2005), maximum single product use exposure is expected for the products: fragrance cream, facial moisturiser, body lotions and hand moisturiser. Exposure to the notified chemical

in these products assuming a bodyweight of 60kg, a 100% dermal absorption factor, a concentration of 3% and that product usage (amount used per use and frequency of use) is similar in Australia to Europe, is as follows:

Fragrance cream: 0.7 mg/kg bw/day
Facial moisturiser: 0.8 mg/kg bw/day
Body lotion: 2.8 mg/kg bw/day
Hand moisturiser: 2.8 mg/kg bw/day

If the notified chemical is used in baby care products, a child's exposure is estimated to be 9.7 mg/kg bw/day assuming a bodyweight of 15kg, a 100% dermal absorption factor, a concentration of 3% and that product usage (amount used per use and frequency of use) is similar in Australia to Europe. Since products containing the notified chemical are stored and used in a domestic environment, there is the possibility of accidental ingestion by a child.

9.2.3. Human health – effects assessment

Acute toxicity
The notified chemical is of low acute toxicity via the oral and dermal routes.

Irritation
Based on the studies provided the notified chemical is considered to be non-irritating to the skin and the eye

Sensitisation
There was limited evidence of sensitisation potential to the notified chemical in the guinea pig maximisation test and no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical in mouse LLNA and no dermal reactions were exhibited during either the induction phase or challenge phase of the repeated Insult Patch Test - human volunteers.
Overall, the notified chemical is considered not to be a potential skin sensitiser.

Repeated Dose Toxicity
In a 28-day oral repeat dose study in rats, a No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day, based on the absence of treatment related effects.

Genotoxicity
The notified chemical was not mutagenic to bacteria and not clastogenic to CHO treated in vitro.

Phototoxicity and Photoallergy
Vital ET (> 50% Disodium Lauriminodipropionate Tocopheryl Phosphate) diluted with water to 5% under semi-occlusive dressing did not induce a response indicative of a phototoxic reaction or a photoallergic reaction.

Hazard classification for health effects.
Based on the available data, the notified chemical is not classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

9.2.4. Occupational health and safety – risk characterisation

Reasonable worst-case exposure to the notified chemical during formulation was estimated to be 3 mg/kg bw/day. Based on a NOAEL of 1000 mg/kg bw/day, derived from a 28-day rat oral study the margin of exposure (MOE) is calculated as 330. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Therefore, the risk of systemic effects using modelled worker data is acceptable for formulation workers.

Following formulation of the end use products, exposure is expected to be very low and as such the risk to workers is also considered to be low.

9.2.5. Public health – risk characterisation

Based on a NOAEL of 1000 mg/kg bw/day, derived from a 28-day rat oral study the margin of exposure (MOE) from a number of exposure scenarios is calculated as follows:

Product(s) used	*Adult/Child*	*Estimated Exposure <mg/kg bw/day>*	*MOE*
Wide range of household, personal care and cosmetic products.	Adult	7.9	130
Fragrance cream	Adult	0.7	1400
Facial moisturiser	Adult	0.8	1300
Body lotion	Adult	2.8	360
Hand moisturiser	Adult	2.8	360
Baby care products	Child	9.7	100

MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. As the all the calculated MOEs are > 100, the risk to public health is considered to be low.

Since products formulated with the notified chemical will be stored and used in a domestic environment, there is also the possibility for children to be exposed to the notified chemical by accidental ingestion. However, as the notified chemical is considered to be of low acute toxicity and given the low concentration of the notified chemical in the formulated products, the risk of lethal effects as a result of accidental ingestion is considered 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 not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

and

As a comparison only, 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.

According to the United Nations (2003) Globally Harmonised System for the Classification and Labelling of Chemicals, a **Chronic II** classification is considered appropriate for the notified chemical.

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio:

The 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 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 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

CONTROL MEASURES
Occupational Health and Safety

- No specific engineering controls, work practices or personal protective equipment are required for the safe use of the notified chemical itself at the concentrations introduced, however, these should be selected on the basis of all ingredients in the formulation.

  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 by landfill.

Emergency procedures

- Spills/release of the notified chemical should be contained with sand or other inert materials.

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(1) of the Act; if
  - the concentration of the chemical as introduced or in the final consumer products has increased, or is likely to increase significantly;

or

(2) 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.

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