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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Sodium Ascorbyl Phosphate

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FULL PUBLIC REPORT

Sodium Ascorbyl Phosphate

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Roche Vitamins Australia Pty Ltd (ABN 36 000 991 793) of Unit C2 1-3 Rodborough Road Frenshs Forest NSW 2086

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)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Yes.

NOTIFICATION IN OTHER COUNTRIES
Germany, France and Switzerland.

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
L-ascorbic acid-2-dihydrogen phosphate, trisodium salt

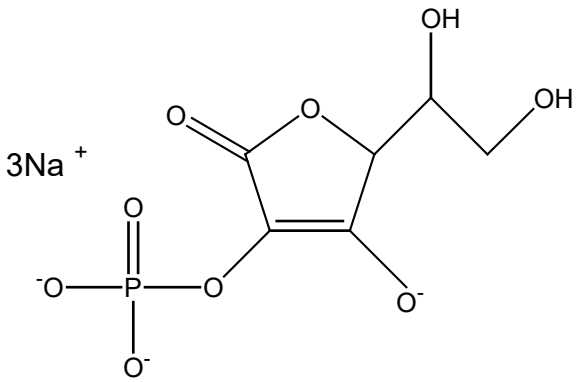
OTHER NAME(S)
Sodium ascorbyl phosphate;
Vitamin C phosphate;
Sodium L-ascorbic acid-2-phosphate;
L-ascorbic acid-2-monohydrogen phosphate, trisodium salt

MARKETING NAME(S)
Stay-C 50

CAS NUMBER
66170-10-3

MOLECULAR FORMULA
$C_6H_6O_9PNa_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
322

SPECTRAL DATA

Remarks No spectral data were provided.

3. COMPOSITION

DEGREE OF PURITY
95%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None.

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)

Chemical Name	sodium pyrophosphate		
CAS No.	7758-16-9	*Weight %*	5

Chemical Name	bis-ascorbyl phosphate		
CAS No.	unknown	*Weight %*	1

ADDITIVES/ADJUVANTS
None.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a raw cosmetic material for formulation in Australia.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.05-1	0.5-1.5	1-1.5	1-1.5	1-1.5

USE
- 2-5% in specialised skin care products for skin lightening;
- 0.5-2% in cosmetics as an antioxidant.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, Transport and Storage

PORT OF ENTRY
Not stated.

IDENTITY OF MANUFACTURER/RECIPIENTS
Roche Vitamins Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia by sea-freight in a shipping container. The chemical will be transported by road from the port of entry to the Roche warehouse for storage. The chemical will then be dispatched to 10 to 30 customer sites in the original 5 kg containers.

5.2. Operation Description

At customer sites, the notified chemical will be used in the formulation of a range of finished cosmetic products such as skin lotions and creams. Formulation usually involves weighing, mixing, and packaging of the finished products. The percentage of the notified chemical in the finished product is expected to vary from 0.5 to 5 %.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Importation and transport	<4		
Storage and distribution	<4		
Weighing	1-2	5 min/day	
Formulation	1-2	5 min/time	
Packaging	2-4	8 hour/day	5 day/week
Cleaning	1-2	0.5-2 hour/batch	

Exposure Details

Transport and storage

There will be 1-2 forklift drivers and 1-2 store persons from the notifier's company, and 1-2 forklift drivers and 1-2 store personnel at the formulation sites involved in transport and storage of the imported notified chemical. However, they are not expected to be exposed to the notified chemical unless the containers are accidentally breached.

Formulation

At the formulation site, weighers will open the container and weigh the notified chemical into another container, which is then sealed prior to transfer to the mixing area. The form of the notified chemical at this stage is a slight dense free flowing powder. The duration of weighing is expected to be about 5 minutes per day.

Formulators will take the weighed up chemical and add the powder into blending vessels. The duration of this transferring is expected to be short (5 minute/batch). The blending vessel is expected to be a closed system. The formulated products will be in liquid or semi-liquid forms containing 0.5-5% notified chemical.

The primary source of exposure to the notified chemical during formulation will be during opening and closing of containers, and weighing and charging the powder into the blending vessel. Inhalation, ocular and dermal exposure may occur during these processes when handling the powder form of the notified chemical. After formulation, dermal contamination would be considered to be the main route of occupational exposure to liquids or semi-liquids. Local exhaust ventilation is in place over the weighing and mixing areas to capture any airborne dust particles or vapours. The notifier states that during formulation operations, weighers and formulators will be attired with suitable industrial clothing, face/eye protection, facemasks, and gloves.

Packaging

Packaging workers will operate the packing machines to fill the finished product from bulk containers into retail packs. They may be exposed to the products containing the notified chemical via dermal contamination since the products are in liquid or semi-liquid form. As the products contain low concentrations of the notified chemical, the exposure is expected to be low. The packaging areas will be fitted with ventilation systems and the packaging workers will wear gloves and safety glasses as a minimum occupational health protection.

Cleaning

Cleaners will be involved in cleaning formulation and packaging equipment including the bulk mixing and storage tanks. Dermal exposure is considered to be the main occupational exposure route for cleaners. As the products are in the liquid or semi-liquid form and contain low concentrations of the notified chemical, the exposure is expected to be low. The notifier states that cleaners will wear

industrial clothing, gloves, face/eye protection or facemasks.

5.4. Release

RELEASE OF CHEMICAL AT SITE
The notifier estimates about 30 kg of the notified chemical may enter the manufacturer's waste treatment facilities each year during manufacturing of the finished products. Wastes may be generated during weighing of the chemical, mixing of the cosmetic product, and washing of mixing vessels and storage tanks used during manufacture of the products. Wastes generated during the manufacturing processes are washed out of tanks and into the on site treatment facilities prior to discharge into the sewer.

RELEASE OF CHEMICAL FROM USE
The notifier estimates that 3% of the notified chemical, equating to about 45 kg per year, may remain in the containers once the product is used up. It is expected that this material will end up in landfill via domestic garbage disposal. The notifier estimates a further 3% will enter the sewer when the products are washed off the consumer's skin in the shower after application.

5.5. Disposal
The notifier does not expect there will be a need for disposal of the unmixed chemical. If disposal is required it will be through a licensed waste disposal contractor.

5.6. Public exposure
Public exposure to the concentrated notified chemical will only occur in the unlikely event of a transport accident or spillage. In the event of an accidental spillage, the chemical should be disposed of in accordance with local, state or federal regulations.

Exposure of the general public to the notified chemical due to industrial processing or accidents could occur in the following cases:

(a) Escape of dust particles into the atmosphere during the formulation process.
(b) Escape of residues into the sewerage system during cleaning up of equipment after manufacturing finished products.
(c) Escape of the chemical into the air, water or soil following an accident.

The possibility of (a) and (b) happening is remote due to controls that manufacturing plants should have in place under existing environmental protection legislation. In the case of (c), exposure is also minimal since the notified chemical is supplied in a small pack size (5 kg) and, in the event of accidental spillage, it is expected that most of the spillage would be cleaned up.

Public exposure to the notified chemical during normal day to day usage of products containing the chemical would be much greater. Finished products containing the notified chemical could be administered to the skin daily or several times a day. Assuming application of a body lotion at 7.5 g, 1-2 times per day, dermal exposure for a 60 kg adult would be approximately 5-10 mg/kg bw/day.

6. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa	A white to slightly of-white powder with very slight odour.
MELTING POINT/BOILING POINT	Not determined.

Remarks The notified chemical started to turn brown above about 245°C but remained solid up to approximately 260°C. It chars before a melting point is reached.

The boiling point could not be determined due to the low vapour temperature.

TEST FACILITY BASF (1997a).

DENSITY 1 940 kg/m^3 at 20ºC

METHOD OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC.
Remarks The relative density was determined by the pycnometer method.
TEST FACILITY BASF (1997a).

VAPOUR PRESSURE $<10^{-8}$ kPa at 20ºC;
$<10^{-7}$ kPa at 130ºC.

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks A vapour pressure test was performed at 130°C over three days, and resulted in no significant loss of weight. Thus the vapour pressure was below the limit of detection of the method. However, assuming a 0.2 mg loss of weight at 130°C, the vapour pressure would be in the order of $<10^{-4}$ Pa, and at 20°C would be $<10^{-5}$ Pa, indicating the notified chemical is not volatile.
TEST FACILITY BASF (1997a).

WATER SOLUBILITY 789 g/L at 20ºC

METHOD EC Directive 92/69/EEC A.6 Water Solubility, Flask Method.
Remarks Following a preliminary test showing water solubility between 53-63 g/100 g, a test was performed using 3 replicates holding the maximum amount of test substance that would allow the mixture to be stirred and having an adequate quantity of undissolved test substance present in the test vessels. The saturated solutions were then filtered and the concentration remaining in the filtrate determined using HPLC. The notified chemical is readily soluble in water.
TEST FACILITY BASF (1997a).

HYDROLYSIS AS A FUNCTION OF PH <5 days at pH 4 and 50°C

METHOD OECD TG 111 Hydrolysis as a Function of pH.
EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.
Remarks Hydrolyses of about 50 mg/L of test substance was performed at pH 4, 7 and 9 and at 50°C. To remove oxygen, nitrogen was allowed to bubble through the solution for 5 minutes prior to analysis. A 30 mL sample of the solution was filtered and placed in vials for heating for the required time period. Concentrations remaining after 3 hours, 24 hours and 5 days were analysed using HPLC. At pH 4 about 70% of the test material was hydrolysed after 5 days, whereas at pH 7 and 9, no degradation was observed.
TEST FACILITY Solvias (2002).

PARTITION COEFFICIENT (n-octanol/water) log Pow at 25ºC = <-4.0

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient, Shake Method.
Remarks Six replicates each containing approximately 54 or 78 mg/L of test substance were each dissolved in 30 mL of water and varying ratios of octanol (75, 150, 300 mL). HPLC was used to determine the concentrations of the test substance in each phase. However no trisodium ascorbate 2-monophosphate was detected in the octanol phases, thus calculations of the partition coefficient were determined using the limit of detection. The results indicate the notified chemical has a poor affinity for lipids and hence should not bioaccumulate.
TEST FACILITY BASF (1997a).

ADSORPTION/DESORPTION Not determined
Remarks The notified chemical is expected to have low to moderate adsorption potential and relatively high mobility in soils.

DISSOCIATION CONSTANT pKa = 3.6 and 7.7

METHOD OECD TG 112 Dissociation Constants in Water.
Remarks The dissociation constant was determined in the pH range 2 to 12. Two constants were determined in this pH range representing the dissociable acid groups.
TEST FACILITY Solvias (2002).

PARTICLE SIZE 10μm (mean particle size).

Remarks Particle size was determined by the laser diffraction method by a Mastersizer 2000 Particle Analyser (Malvern Instruments).
TEST FACILITY Not provided.

FLASH POINT Not determined.

Remarks Not applicable for a solid.

FLAMMABILITY LIMITS Not highly inflammable.

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks Fire did not spread under the test conditions.
TEST FACILITY BASF (1997a)

AUTOIGNITION TEMPERATURE 238ºC

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
TEST FACILITY BASF (1997a).

EXPLOSIVE PROPERTIES Non-oxidising.

Method 92/69/EEC A.17
Remarks A burn rate of 0.11 mm/sec was observed for a mixture containing 30% notified chemical.

The notified chemical does not present any risk of explosion because it is incapable of decomposing, forming gases or release heat very rapidly.
TEST FACILITY BASF (1997a).

REACTIVITY Not determined.

Remarks The notified chemical is incapable of reaching exothermically with a combustible material based on its structural formula.

SURFACE TENSION 69.5 mN/m at 20ºC and 1 g/L

METHOD EC Directive 92/69/EEC A.5 Surface Tension, Ring Method
Remarks The notified chemical is not surface active.
TEST FACILITY BASF (1997a).

7. TOXICOLOGICAL INVESTIGATIONS

9.2.3.1 SUMMARY OF TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 >5 000 mg/kg bw	low toxicity
Rat, acute dermal LD50 > 2 000 mg/kg bw	low toxicity
Rat, acute inhalation	No data provided
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation - adjuvant test	limited evidence of sensitisation.

Rat, drinking water Repeat Dose Toxicity - 28 Days.	NOAEL=5 000 ppm (424.1 mg/kg bw/day) in males, NOAEL=1 000 ppm (90.3 mg/kg bw/day) in females.
Genotoxicity - bacterial reverse mutation	Non mutagenic
Genotoxicity – in vitro chromosomal aberration	Non genotoxic
Genotoxicity – in vivo	No data provided

7.1. Acute toxicity – oral

TEST SUBSTANCE	Sodium ascorbyl phosphate
METHOD	OECD TG 401 Acute Oral Toxicity – Limit Test. EC Directive 92/69/EEC B.1 Acute Toxicity (Oral) – Limit Test.
Species/Strain	Rat/Wistar
Vehicle	Water.
Remarks - Method	GLP & QA.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	5 000	0/10

LD50	> 5 000 mg/kg bw
Signs of Toxicity	After treatment, both males and females had impaired or poor general state, dyspnoea, apathy, staggering and diarrhoea up to 5 hours. The animals appeared normal 1 day after treatment.
Effects in Organs	None.
Remarks - Results	None.

CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	BASF (1997b).

7.2. Acute toxicity - dermal

TEST SUBSTANCE	Sodium ascorbyl phosphate
METHOD	OECD TG 402 Acute Dermal Toxicity– Limit Test. EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain	Rat/Wistar
Vehicle	Water.
Type of dressing	Semi-occlusive.
Remarks - Method	GLP & QA.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	2 000	0/10

LD50	> 2 000 mg/kg bw
Signs of Toxicity - Local	Very slight erythema was seen in 2 males and 2 females on day 1.
Signs of Toxicity - Systemic	None.
Effects in Organs	None.
Remarks - Results	None.

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

TEST FACILITY BASF (1998a).

7.3. Acute toxicity - inhalation

No study was provided for assessment.

7.4. Irritation – skin

TEST SUBSTANCE Sodium ascorbyl phosphate

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	None.
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	GLP & QA.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	0.56	2	48 hour	0
Oedema	0	0	-	0

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

Remarks - Results PII (Primary irritation index) = 0.75

CONCLUSION The notified chemical is slightly irritating to skin.

TEST FACILITY BASF (1997c).

7.5. Irritation - eye

TEST SUBSTANCE Sodium ascorbyl phosphate

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

Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Observation Period	72 hours
Remarks - Method	GLP & QA. Test material was washed out 24 hours after treatment.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0.83	2	48 hours	0
Conjunctiva: chemosis	0.11	1	48 hours	0
Conjunctiva:discharge	0	2	1 hour	0
Corneal opacity	0	-	-	0
Iridial inflammation	0	-	-	0

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

Remarks - Results None.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY BASF (1997d).

7.6. Skin sensitisation

TEST SUBSTANCE Sodium ascorbyl phosphate

METHOD OECD TG 406 Skin Sensitisation – maximisation test.
EC Directive 96/54/EC B.6 Skin Sensitization - maximisation test.

Species/Strain Guinea pig/Pirbright white

PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: <5%
topical: >50%

MAIN STUDY

Number of Animals induction phase Test Group: 30 Control Group: 10 per group
Induction Concentration:
intradermal injection 5%
topical application 50%

Signs of Irritation All the test animals had well-defined erythema (grade 2) and/or oedema (grade 2) after intradermal injections and percutaneous induction.

CHALLENGE PHASE

1st challenge topical application: 50%

2nd challenge topical application: 50%

Remarks - Method GLP & QA.

Water was used as the vehicle.

Positive controls were not included in this study. The laboratory runs positive control tests twice a year.

Rationale in using two control groups is that in the event of borderline results after the first challenge the first control group cannot be re-used; the second control group was used exclusively for the second challenge.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	50%	4/23	4/23	0/23	0/23
Control Group 1	50%	0/10	0/10	0/10	0/10
Control Group 2	50%			0/10	0/10

Remarks - Results Seven test animals died at days 8, 9 and 10 before the first challenge. A macroscopic examination revealed the deaths were due to pneumonia and were not related to treatment of the notified chemical.

CONCLUSION There was limited evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY BASF (1997e).

7.7. Repeat dose toxicity

TEST SUBSTANCE	Sodium ascorbyl phosphate
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat/Wistar
Route of Administration	Oral –drinking water.
Exposure Information	Total exposure days: 28 days; Dose regimen: 7 days per week; Post-exposure observation period: 14 days
Vehicle	Water
Remarks - Method	GLP & QA.

RESULTS

Group	*Number and Sex*	*Dose/Concentration*		*Mortality*
		Nominal (ppm)	*Actual (mg/kg/day)*	
Control	5/sex	0	-	0
Control (recovery)	5/sex	0	-	0
Low	5/sex	1 000	86.6 (combined) 82.8 (males), 90.3 (females)	0
Mid	5/sex	5 000	468.1 (combined) 424.1 (males), 512 (females)	0
High	5/sex	15 000	1543.9 (combined) 1426 (males), 1661.7 (females)	0
High (recovery)	5/sex	15 000	1634.2 (combined) 1380.8 (males), 1887.5 (females)	0

Mortality and Time to Death
No animal died during the study.

Clinical Observations
No abnormal clinical findings were observed.

No treatment-related effects were observed in food consumption, bodyweight data, food efficiency, functional observational battery, and motor activity measurement. Water consumption was increased in high-dose animals on day 27 (main and recovery males) and days 7-27 and 42 (recovery group females).

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No treatment-related changes were found in haematology, clinical chemistry, and urinalyses. Some marginal, incidental and inconsistent deviations were seen. However, these findings are considered to be of no toxicological significance when compared with the other sex, or lack dose-response relationship.

Effects in Organs
The absolute weight of ovaries was decreased in high-dose females. Gross lesions were noted in the glandular stomach of a mid-dose male (focus) and in a control female (erosion/ulcer) in the liver (focus) and lungs (focus) of a mid-dose male, and in the iliac lymph nodes of a control male (discolouration).

Histopathological examination found treatment-related effects in the urinary bladder of male rats and in the thymus of female rats. Moderate to severe focal/multifocal or diffuse hyperplasia of the transitional cells in the urinary bladder was observed in all high-dose males. Four high-dose males had slight to moderate cystitis and one of them had a focal ulceration in the hyperplastic epithelium. Slight multifocal hyperplasia of the transitional cells was also recorded in one high-dose female. Slight increase of starry sky cells in the cortex of the thymus was noted in 4 high-dose females and 3 mid-dose females. No morphologic correlate was obtained for the decreased mean weight of the ovaries in high-dose animals.

In the high-dose recovery group, the only gross lesion noted was in the glandular stomach of a female. Histopathological examination revealed an incidental focus of cystic malformation, which was correlated

with the gross lesion in the glandular stomach.

Remarks – Results

The following effects are considered to be treatment related observed in this study.

At the high-dose

- Increased water consumption in males and females.
- Focal or diffuse hyperplasia of the transitional epithelium in the urinary bladder of all males.
- Cystitis in 4 males.
- Increased number of starry sky cells in the cortex of the thymus of 4 females.

At the mid-dose

- Increased number of starry sky cells in the cortex of the thymus of 3 females

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 5 000 ppm (424.1 mg/kg bw/day) for males and 1 000 ppm (90.3 mg/kg bw/day) for females in this study.

TEST FACILITY BASF Aktiengesellschaft (1998b).

7.8. Genotoxicity - bacteria

TEST SUBSTANCE Sodium ascorbyl phosphate

METHOD OECD TG 471 & 472 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure and Pre incubation procedure.

Species/Strain *S. typhimurium*: TA1535, TA1537, TA98, TA100.
E. coli: WP2 uvrA.

Metabolic Activation System S9-mix

Concentration Range in Main Test a) With metabolic activation: 0-6 000 µg/plate.
b) Without metabolic activation: 0-6 000 µg/plate.

Vehicle Water

Remarks - Method GLP & QA.

Plate incorporation procedure was used in the first test and pre-incubation procedure was used in the second test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in PreliminaryTest	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present				
Test 1		>3 000	None	None
Test 2		>3 000	None	None
Absent				
Test 1		>3 000	None	None
Test 2		>3 000	None	None

Remarks - Results A slight decrease in the number of revertants was occasionally observed depending on the strain and test conditions from about 3 000 µg/plate onwards.

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

TEST FACILITY BASF Aktiengesellschaft (1997f).

7.9. Genotoxicity – in vitro

TEST SUBSTANCE	Sodium ascorbyl phosphate
METHOD	OECD TG 473 In vitro Mammalian Chromosomal Aberration Test.
Cell Type/Cell Line	Chinese hamster V79 cells
Metabolic Activation System	S9-mix
Vehicle	Water
Remarks - Method	GLP & QA.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period (hr)*	*Harvest Time (hr)*
Present			
Test 1	125, 250, 500*, 1 000, 2 000* and 3 800*	4	18
	500, 1 000, 2 000 and 3 800*	4	28
Test 2			
	No test		
Absent			
Test 1	125, 250, 500*, 1 000, 2 000* and 3 800*	4	18
	500, 1 000, 2 000 and 3 800*	4	28
Test 2	125, 250, 500*, 1 000, 2 000* and 3 800*	18	18
	500, 1 000, 2 000* and 3 800	28	28

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in PreliminaryTest	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present	None			
Test 1		>3 800	None	None
		>1 000	None	None
Test 2				
Absent	>31 25			
Test 1		>1 000	None	None
		>3 800	None	None
Test 2		>3 800	None	None
		>1 000	None	None

Remarks - Results	In both experiments, neither a statistical significant nor a biological relevant increase in the number of cells carrying structural chromosomal aberration was observed after treatment with the test material. No increase in the frequencies of pyloploid metaphases was found after treatment with the test material as compared to that of the controls.
CONCLUSION	The notified chemical was not clastogenic to Chinese hamster V79 cells treated in vitro under the conditions of the test.
TEST FACILITY	Cytotest Cell Research GMBH (1998).

7.10. Genotoxicity – in vivo

No study was provided for assessment.

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE	Sodium ascorbyl phosphate
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sludge containing non-adapted micro-organisms from laboratory wastewater treatment plant, which were fed with municipal and synthetic sewage.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	TOC, DOC
Remarks - Method	In addition to 100 mg/L of the test substance, blank samples and samples containing a reference substance were measured.

RESULTS

Test substance		*Aniline*	
Day	*% degradation*	*Day*	*% degradation*
6	20	6	60
10	20-30	10	80
28	20-30	28	80

Remarks - Results	From 20-30% of the test substance was degraded after 28 days, compared to 80-90% of the reference substance, aniline, degraded after 10 days. Degradation of the reference substance indicates the test system was valid.
CONCLUSION	The notified chemical is not readily biodegradable according the OECD criteria requiring >60% degradation after 10 days.
TEST FACILITY	BASF (1997g).

8.1.2. Bioaccumulation

No bioaccumulation data were available. The low molecular size of the chemical could enable it to cross biological membranes. However, the log P_{ow} indicates the chemical has a poor affinity to lipids and hence is not likely to diffuse across biological membranes and bioaccumulate, but rather will remain in the water. It is expected the vitamin C phosphate groups would be readily metabolised if ingested by organisms.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE	Sodium ascorbyl phosphate
METHOD	EEC Directive 84/449, part C.1 Acute Toxicity for Fish - 96 hour/static conditions.
Species	Zebra fish (*Brachydanio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Test concentrations were analysed using ion pair chromatography
Remarks – Method	The test solution was coloured yellow by the test substance, and the colour increased with increasing concentrations.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	<1	10	0	0	0	0	0
50	50.7	10	0	0	0	0	0
100	104	10	0	0	0	0	0
1000	1040	10	0	0	0	0	0
2150	2230	10	0	0	0	0	0
4640	4800	10	0	3	3	3	3
10000	11000	10	5	10	10	10	10

LC50	5343 mg/L at 96 hours.
NOEC (or LOEC)	2150 mg/L at 96 hours.
Remarks – Results	All fish died when exposed to the highest test concentration. Eight fish exhibited a narcotic-like state after 4 hours of exposure to concentrations of 4640 mg/L and 5 fish exhibited swimming near the surface within the first hour after exposure to the highest test concentration.

CONCLUSION The notified chemical is not toxic to Zebra fish (Mensink *et al.,* 1995)

TEST FACILITY BASF (1998c).

8.2.2. Acute/chronic toxicity to aquatic invertebrates

TEST SUBSTANCE

METHOD	EEC Directive 79/831/EEC, Annex V, Part C.2 Acute Toxicity for Daphnia – 48 hour static test.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	2.20 – 3.20 mmol/L
Analytical Monitoring	Test concentrations using ion pair chromatography
Remarks - Method	The pH of the test solution was within the range 7.9-8.1

RESULTS

Concentration mg/L		*Number of D. magna*	*Number mobile*	
Nominal	*Actual*		*24 h*	*48 h*
0	<2	20	20	20
12.5	14	20	20	19
25	-	20	20	20
50	-	20	20	20
100	105	20	20	20

LC50	>100 mg/L at 48 hours
NOEC (or LOEC)	Not reported
Remarks - Results	

CONCLUSION The test substance is very slightly toxic to daphnia (Mensink *et al.,* 1995).

TEST FACILITY BASF (1997h).

8.2.3. Algal growth inhibition test

TEST SUBSTANCE Sodium ascorbyl phosphate

METHOD	EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range Nominal	Eleven concentrations between 0.1 to 100 mg/L using a dilution factor of two.
Concentration Range Actual	0.1 to 98.2 mg/L measured at the start and end of the test for the following concentrations: 125 (stock solution), 100, 3.13, 0.1 and 0 (control) mg/L.
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	Test concentration using ion pair chromatography
Remarks - Method	The pH of the test system varied between 7.9 at the start and 9.5 at the end of the test.

RESULTS

Effect	*Biomass mg/L at 72 h*	*Growth mg/L at 0-72 h*
EC_{10}	15.7	76.2
EC_{50}	100	100
EC_{90}	100	100
LOEC	6.25	6.25
NOEC	3.1	3.1

Remarks - Results	The notified chemical inhibited biomass by 40% and growth rate by 10% at the highest test concentration.
CONCLUSION	The notified chemical is very slightly toxic to green algae (Mensink *et al.,* 1995).
TEST FACILITY	BASF (1998d).

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Sodium ascorbyl phosphate
METHOD	DIN EN ISO 10712 (February 1996).
Inoculum	*Pseudomonas putida*
Exposure Period	16 hours
Concentration Range Nominal	Nine concentrations between 39.1 to 10000 mg/L using a dilution factor of two.
Remarks – Method	The EC50 of the control substance, 3,5-dichlorphenole was 18.7 mg/L.
RESULTS	
IC50	7700 mg/L
NOEC	Not reported.
Remarks – Results	Microorganisms, contained in tubes of glass plugged with gas permeable silicone sponge caps, were exposed to nominal concentrations of the test substance, and after 16 hours, their cell densities were determined and compared to untreated controls. The test substance caused a strong increase (25%) in bacterial cell multiplication in the concentration range between 313 and 2500 mg/L compared to the untreated control. Above a concentration of 2500 mg/L inhibition of cell multiplication occurred.
CONCLUSION	The test substance was not toxic to the aerobic bacterium *Pseudomonas putida*.
TEST FACILITY	BASF (1997i).

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notifier estimates about 75 kg of the notified chemical may enter the sewer each year as a result of usage of the cosmetic products, when the products are washed off the skin during bathing and during manufacturing of the products. A further 45 kg of waste may enter landfill as residues in containers.

The notified chemical is highly water-soluble and hence, in sewage treatment plants, is expected to partition mainly into the water compartment. The partition coefficient indicates the chemical will have little affinity for organic matter in the environment, and hence adsorption onto sewage sludge is not expected. The low vapour pressure indicates the chemical is not volatile, and hence no partitioning into the atmosphere from water is expected.

It is difficult to predict how much of the chemical will be absorbed by the skin and how much will be removed in the shower. We have calculated a worst-case scenario daily PEC for the aquatic environment resulting from release at end use of products, assuming that all of the product containing the notified chemical is removed in the shower during bathing, with no skin absorption. In calculating the PEC, we have also assumed that release to sewage systems occurs on a nationwide basis and is continuous throughout the year. The assumptions are summarised below:

- All of the 1500 kg of chemical imported in one year is released into the sewer over a 365-day period, with no removal of the chemical by adsorption or degradation, giving a daily release of 4100 g.

- Release is distributed throughout the whole country, with a sewer output based on 18 million people using water at an average volume of 150 L per day per person, giving a daily sewer output of 2700 ML.

The nationwide PEC of the notified chemical in sewer is 1.5 X 10^{-3} mg/L (or 1.5 µg/L) per day. This PEC would be further diluted once released into the receiving waters by an amount that will depend on the nature of the receiving waters (eg. ocean, river, flow rate).

9.1.2. Environment – effects assessment

The results of the toxicity tests indicate the notified chemical is not toxic to fish, daphnia or algae, with all organisms having LC_{50} values greater than 100 mg/L. The test chemical was able to inhibit the multiplication of the soil and water bacterium, *Pseudomonas putida*, only at very high concentrations (i.e. 7700 mg/L). A PNEC (predicted no effect concentration) calculated using the LC50 of the most sensitive species and a safety factor of 100 would be >1.0 mg/L

9.1.3. Environment – risk characterisation

Usage patterns indicate that the most of the notified chemical could eventually be released into the aquatic environment via sewage treatment facilities when the cosmetic products are washed off the skin during bathing. However, release is expected to occur in a diffuse manner owing to the nationwide use of the products.

The notified chemical is highly water-soluble and hence, in sewage treatment plants, is expected to partition mainly into the water compartment. The chemical is not readily biodegradable, with only 20-30% degradation after 28 days, and so is not likely to be eliminated in the sewer prior to its release into the natural environment.

The notified chemical is not toxic to aquatic organisms, with fish, daphnia and algae all having an LC_{50} greater than 100 mg/L. A worst-case daily PEC calculated, assuming all of the yearly import volume is released into the sewer in a diffuse manner, is 1.5 X 10^{-3} mg/L. The PEC/PNEC ratio is significantly less than one, indicating no immediate concern toward the

environment. The calculated PEC would be further reduced once released into the receiving waters, further reducing aquatic exposure.

9.2. Human health

9.2.1. Human health - effects assessment

Acute Toxicity
The notified chemical was of low acute oral and dermal toxicity.

Irritation and Sensitisation.
The notified chemical was a slight skin irritant and a slight eye irritant in rabbits. There was limited evidence that the notified chemical was a mild sensitiser in guinea pigs.

Repeated Dose Toxicity (sub acute, sub chronic, chronic).
The notified chemical was administrated to male and female rats in drinking water for 4 weeks at concentrations of 0. 1 000, 5 000 and 15 000 ppm. The control and high-dose groups had extra 5/sex animals, which were maintained for 14 days without administration of the notified chemical after the treatment.

Several effects are considered to be treatment related observed in this study. At the high-dose, changes were observed in increased water consumption in males and females, focal or diffuse hyperplasia of the transitional epithelium in the urinary bladder of all males, cystitis in 4 males, and increased number of starry sky cells in the cortex of the thymus of 4 females.

At the mid-dose, the only treatment related effect was increased number of starry sky cells in the cortex of the thymus of 3 females.

NOAEL of 5 000 ppm (424.1 mg/kg bw/day) for males, and 1 000 ppm (90.3 mg/kg bw/day) for females were established based on the treatment related effects.

Genotoxicity
No evidence of genotoxicity in Ames test and chromosomal aberration assay.

9.2.2. Occupational health and safety – risk characterisation

During transport, storage and distribution of the notified chemical and products containing the notified chemical, there is unlikely to be any worker exposure, except in the event of an accidental spill. Exposure after a spill should be controlled by the recommended practices for cleaning up of spills stated in the Material Safety Data Sheet (MSDS).

During formulation processes, there is potential for dermal, ocular and inhalation exposure to the powder form of the notified chemical when weighing the notified chemical and charging it to the blending vessels. Of particular concern would be respiratory irritation, as the mean particle size of the notified chemical was measured as 10 μm, so some of the particles may be within the respirable range. To avoid adverse health effects of high concentration of dust in the workplace, good hygiene practices should be adopted to minimise airborne dust levels. Exposure to the dust in the workplace should be controlled below the NOHSC exposure standard for dusts (NOHSC, 1995). The notifier indicated that at formulation sites, the inhalation exposure to the notified chemical will be reduced due to the use of local exhaust ventilation over weighing, mixing and filling areas and general ventilation in rest of the work area. Additionally, since the notified chemical was a mild skin sensitiser in guinea pigs, the workers should wear industrial clothing, gloves and eye protections to minimize dermal and/or ocular exposure.

Dermal exposure may also occur during packaging the formulated products and cleaning the mixer vessels and packaging machines. Packaging and cleaning workers would be exposed only to the formulated products containing less than 5% notified chemical. These workers should wear personal protective equipment including industrial clothing, gloves and eye protections.

The notifier states that the workers will receive education and training on safe use of dusty products and preventive controls. This, in combination with engineering controls and personal protective equipment, will reduce the occupational exposure to the notified chemical. Consequently the adverse health risk to workers at the formulation sites is considered to be low.

9.2.3. Public health – risk characterisation

Exposure of the general public to the notified chemical as a result of transport or through environmental release is assessed as being negligible. Although members of the public will make frequent dermal contact with products containing the notified chemical, the risk to public health is considered to be minimal since the notified chemical has low acute oral and dermal toxicity with no irritating effects on the skin and eyes. The above conclusion is also supported by the statement that the products containing the notified chemical have been used in other countries with no documented adverse effects to date.

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 (NOHSC, 1999).

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio, the low environmental exposure and low toxicity to aquatic organisms: 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 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, 1994a). 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, 1994b). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:

- Local exhaust ventilation at the formulation sites.

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Industrial hygiene practices should be adopted to minimise airborne dust levels.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Industrial clothing,
  - Gloves, and
  - Eye protection.

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

- Atmospheric monitoring should be conducted to measure workplace dust concentrations during formulation of the notified chemical.

- 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 incineration or in landfill.

Emergency procedures

- Spills/release of the notified chemical should be collected and disposed of by incineration.

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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