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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Tinovis GTC (Acrylates/Beheneth-25 Methacrylate Copolymer)

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

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

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

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Director
NICNAS

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FULL PUBLIC REPORT

Tinovis GTC (Acrylates/Beheneth-25 Methacrylate Copolymer)

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Ciba (Australia) Pty Ltd (ABN 97 005 061 469)
235 Settlement Rd, THOMASTOWN VIC 3074

NOTIFICATION CATEGORY
Limited: Synthetic polymer with Mn ≥ 1000 Da.

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:

Chemical Name, Other Names, CAS Number, Molecular and Structural Formulae, Spectral Data, Methods of Detection and Determination, Molecular Weight, Purity, Identity and % Weight of Toxic or Hazardous Impurities, Non-hazardous Impurities, Identity and % Weight of Additives/Adjuvants, Import Volume, Identity of Customers and Sites, Polymer Constituents.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:

Melting Point, Boiling Point, Specific Gravity, Vapour Pressure, Water Solubility, Hydrolysis as a Function of pH, Partition Co-efficient, Adsorption/Desorption, Dissociation Constant, Particle Size, Flash Point, Flammability Limits, Autoignition Temperature, Explosive Properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
China (2004)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Tinovis GTC (containing approximately 30% of the notified polymer)

OTHER NAME(S)
Acrylates/Beheneth-25 Methacrylate Copolymer (INCI name)
TINOVIS GT Clear
Acrylate polymer dispersion in water
FAT 55558/B
DP705-9319

MOLECULAR WEIGHT (MW)
Number Average Molecular Weight (Mn) > 1000 Da

ANALYTICAL DATA
Reference IR, GPC, UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY > 95%

LOSS OF MONOMERS, OTHER REACTANTS, ADDITIVES, IMPURITIES

No degradation, decomposition or depolymerisation of the notified polymer is expected to occur under normal conditions of use.

Thermal decomposition may release toxic fumes such as carbon monoxide and carbon dioxide.

DEGRADATION PRODUCTS
No losses by volatilisation, exudation or leaching are expected.

4. PHYSICAL AND CHEMICAL PROPERTIES

The notified polymer is to be imported as an aqueous dispersion of the water insoluble polymer: Tinovis GTC. Physico-chemical properties are known for the dispersion. Glass transition temperature and dissociation constant have been estimated for the notified polymer.

APPEARANCE AT 20°C AND 101.3 kPa: White liquid with a slight acrylate odour (dispersion)

Property	Value	Data Source/Justification
Glass Transition Temperature	38 - 88°C	Estimated for notified polymer
Density	1030 kg/m^3	MSDS
Vapour Pressure	Not determined	Negligible due to the high molecular weight of the notified polymer.
Viscosity	50 mPa.s (25°C)	MSDS
Water Solubility	0.35 g/L at 20°C	Measured at pH 5
Hydrolysis as a Function of pH	Not determined	Hydrolysis is not expected at the environmental pH range of 4 – 9, despite the presence of hydrolysable functionalities in the notified polymer.
Partition Coefficient (n-octanol/water)	Not determined	A relatively low value of P_{OW} is expected based on the hydrophilic structure and the water solubility of the notified polymer.
Adsorption/Desorption	Not determined	Not expected to significantly absorb to organic matter and soils rich in organic carbon based on the relatively hydrophilic structure of the notified polymer.
Dissociation Constant	Not determined	Contains anionic groups expected to have a pKa value of 3~5, and will be ionised in the environmental pH range of 4-9.
Particle Size	Not determined	Supplied as aqueous dispersion.
Flash Point	Not determined	High molecular weight polymer.
Autoignition Temperature	Not determined	Supplied as aqueous dispersion.
Explosive Properties	Not determined	High molecular weight polymer without any chemical moieties that would contribute to the polymer being explosive.

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

Reactivity

Expected to be stable under normal environmental conditions. The polymer is not resistant to freezing temperature and it is sensitive to heat.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified polymer will not be manufactured in Australia. It will be imported into Australia by sea at a level

of approximately 30% in the sales product Tinovis GTC.

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

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

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
Ciba (Australia) Pty Ltd
235 Settlement Road
Thomastown VIC 3074

TRANSPORTATION AND PACKAGING
The notified polymer will be imported in UN approved 25 kg closed head plastic drums as a component of polymer dispersion Tinovis GTC at a concentration of approximately 30%. The polymer dispersion will be transported by road from wharf to a contracted warehouse in Melbourne prior to distribution by road to cosmetic formulators, where products containing the polymer will be packed in a variety of glass and plastic bottles and jars ranging from 50 to 500 mL in size. The products will be distributed by road to retail outlets and hair salon outlets. The notified polymer will be present in the cosmetic products at a concentration of 0.3 to 1.5%.

USE
Component of cometic products. The notified polymer is used as rheology modifier for clear gel systems in cosmetics, e.g. skin and hair care formulations.

OPERATION DESCRIPTION
The notified polymer will be imported into Australia as a dispersion in water containing approximately 30% notified polymer. During warehousing and shipping, workers will handle the polymer dispersion in their original packaging in sealed plastic drums.

The polymer dispersion will be distributed to cosmetic formulators for reformulation into cosmetic products. During reformulation, the polymer dispersion will be gravity fed or pumped from the plastic drums into a stainless steel mixing vessel of 500 to 2000 L capacity. Alternatively, the polymer dispersion will be weighed and the required amount is manually poured into the stainless steel mixing vessel. Mixing is achieved by slow mechanical stirring. Other ingredients will be added and the resulting mixture is tested for quality control.

The formulated cosmetic product will be pumped from the mixing vessel to a holding tank prior to packaging in 50 to 500 mL containers. Filling and packaging operations are automated and enclosed, and involve automated filling, capping and labelling. The cosmetic products will contain 0.3 to 1.5% notified polymer.

The cosmetic products containing the notified polymer will be sold to retail outlets for consumer use and will also be available to hair salons. Hairdressers, beauticians and similar workers will apply the cosmetic products to hair and skin of clients.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and warehouse	5 – 10	1 hour per day	30 – 60 days per year
Laboratory technicians	5 – 10	4 hours per day	30 – 60 days per year
Weighing operations	1 – 5	1 hour per day	30 days per year
Manufacturing operations	5 – 10	2 – 4 hours per day	30 – 60 days per year

Salon workers	100	0.5 hours per day	100 days per year

EXPOSURE DETAILS

Transport and Storage

The notified polymer will be transported from the wharf to the contracted warehouse, and then to the formulators in UN-approved drums designed to withstand impact and minimise breakage in the event of an accident. Occupational exposure for warehouse staff involved in handling, transporting and storing Tinovis GTC is not expected, except in the case of an accident.

Formulation and Quality Control

During formulation, Tinovis GTC will be handled in relatively small quantities (level of addition in products containing the notified polymer is 1 – 5%, equivalent to 0.3 – 1.5% notified polymer) by gravity feed or pumping from the plastic drums into a stainless steel mixing vessel. The polymer dispersion may also be weighed and the required amount manually poured into the stainless steel mixing vessel. Manufacturing operators may have dermal or ocular exposure to the notified polymer if there are spills during manual pouring or pumping. Manufacturing operators will wear coveralls, impervious gloves and safety goggles.

Laboratory technicians may have dermal or ocular exposure to the notified polymer at 30% through spills which may occur during sampling of the Tinovis GTC containing the notified polymer at 30%. They may also have dermal or ocular exposure to the notified polymer at concentrations between 0.3 – 1.5% through spills or splashes which may occur when sampling the formulated product.

Packaging

Packaging workers will not be exposed directly to Tinovis GTC. They may, however, have ocular or dermal exposure to the notified polymer at concentrations between 0.3 % and 1.5% through spills or splashes which may occur when transferring the formulated product to the jars and bottles.

Salon

Salon workers, such as hairdressers, beauticians and similar workers may experience frequent dermal and ocular exposure to the notified polymer if involved in the application of products containing the notified polymer to the consumers. The extent of this exposure is likely to be comparable to the exposure of the consumers who would use the same products.

6.1.2. Public exposure

Public exposure to the notified polymer is expected to be widespread and frequent through daily use of personal care products containing the notified polymer at concentrations up to 1.5%.

The principal route of exposure is dermal, with deliberate application over the skin. Eye exposure is also possible during the use and application of the face and body skin products. Oral exposure from the use of these types of products is unlikely and only possible in case of accidental ingestion. Some inhalation exposure could occur if the polymer was used in cosmetic spray products.

6.2. Human health effects assessment

The results from toxicological investigations conducted on Tinovis GTC containing approximately 30% of the notified polymer are summarised in the table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	oral LD50 > 5000 mg/kg bw low toxicity
Rat, acute dermal toxicity	LD50 > 5000 mg/kg bw low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test (2 studies).	no evidence of sensitisation
Rat, repeat dose oral toxicity – 5 days.	No Observed Adverse Effect Level (NOAEL) cannot be established
Mutagenicity – bacterial reverse mutation	non mutagenic

Toxicokinetics, Metabolism and Distribution.
Based on the data submitted, dermal absorption of the notified polymer is expected to be limited due to its high molecular weight, relatively hydrophilic structure. The polymer is expected to become more hydrophilic at higher pH as the acid groups ionise. As the notified polymer contains < 15% of low molecular weight species < 1000 Da and < 10% of species < 500 Da, the dermal absorption of these low molecular species cannot be ruled out. However, the dermal absorption of the notified polymer is not expected to exceed 10%.

Acute Toxicity.
The acute toxicity of Tinovis GTC containing 30% of the notified polymer was determined to be low when administered by the oral and dermal route.

Irritation and Sensitisation.
Tinovis GTC containing 30% of the notified polymer was slightly irritating to the skin and eyes in rabbits.

Skin sensitising potential of Tinovis GTC containing 30% of the notified polymer was assessed in two adjuvant Magnusson-Kligman tests with guinea pigs, Tinovis GTC containing 30% of the notified polymer did not show sensitising reactions.

Repeat Dose Oral Toxicity.
The toxicity related to repeated exposure to Tinovis GTC containing 30% of the notified polymer was examined in a preliminary 5-day repeat dose oral toxicity test in rats at three doses between 200 and 2000 mg/kg bw/day. During the study, no deaths occurred and no adverse effects were observed. NOAEL cannot be established on the limited data.

Mutagenicity
The mutagenic potential of Tinovis GTC containing 30% of the notified polymer was assessed in a reverse mutation test in bacteria and the result was negative. Based on this study Tinovis GTC containing 30% of the notified polymer is not considered mutagenic.

No other toxicity studies were available for the notified polymer or Tinovis GTC.

Classification
Based on the available data the notified polymer cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
Based on the available data, Tinovis GTC containing approximately 30% of the notified polymer is slightly irritating to skin and eyes.

Warehouse and transport workers may have dermal, ocular and inhalation exposure in case of accident when Tinovis GTC containing the notified polymer (approximately 30%) is imported and transported in Australia. In such a case there will be a risk of slight skin and eye irritation. Employment of standard hygiene practices will minimise skin contact (including the use of appropriate gloves and protective clothing and eye protection). The Material safety Data Sheet (MSDS) should inform workers about the potential hazards of the notified polymer. The likelihood of accidental exposure to the notified polymer during transport and storage is considered to be low and thus the corresponding risk is considered low.

Dermal, ocular and inhalation exposure to high concentrations of the notified polymer (approximately 30%) is also possible for workers involved in formulation and quality control testing of consumer products. However, worker exposure is expected to be low due to the standard industrial hygiene practices and the use of personal protective equipment (PPE). Therefore, the risk of adverse effects for formulators and workers involved in quality control testing is considered to be low.

Workers involved in packaging of the finished consumer products may encounter dermal and ocular exposure to the notified polymer at significantly lower concentrations (<1.5%). Considering the limited opportunity for direct contact with the notified polymer and the use of PPE such as safety glasses and gloves for skin and eye protection, the risk is low.

The risk for salon workers is expected to be similar to that of the public, discussed in the following section.

6.3.2. Public health

Members of the public will have widespread and frequent exposure to the notified polymer through daily use of personal care products containing it. The principal route of exposure is dermal, with deliberate application over the skin. Eye exposure is also possible during the use and application of the face and body skin products. Based on available data the main risks associated with this pattern of use of the notified polymer are related to skin and eye irritation.

The risk of eye irritation during use of products containing the notified polymer is assessed as low due to its expected low direct contact and the low concentration of the notified polymer in the finished product.

Skin irritation may occur based on the exposure pattern of the public to products containing the notified polymer. However, the risk is minimised by the low concentration of the notified polymer in the products for personal use (< 1.5%). Safety warning advising discontinuation of use in case of development of skin irritating reactions would also help in minimising risk of serious adverse reactions related to skin irritation.

No adverse effects were observed in a preliminary 5-day repeat dose oral toxicity study at up to 2000 mg/kg bw/day of Tinovis GTC (600 mg/kg bw/day of the notified polymer). Although a NOAEL for repeated exposure cannot be established on the basis of limited data, it is noted that limited systemic exposure is expected because of the high molecular weight. However, some low molecular weight species are present.

Overall, based on the available data the notified polymer in cosmetic products is not considered to pose an unreasonable risk at concentrations up to 1.5%.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified polymer will be imported in UN-approved 25 kg closed head plastic drums as a component of polymer dispersion in water, and will be further reformulated into cosmetics products in Australia.

During formulation of cosmetic preparations, the estimated annual losses of notified polymer are:

Spills	< 1 %	< 10 kg
Equipment cleaning	< 2 %	< 20 kg
Import container residuals	< 1 %	< 10 kg
Total annual loss due to formulation		< 40 kg

RELEASE OF CHEMICAL FROM USE

The majority (up to 95%) of the notified polymer will be incorporated into the cosmetic preparations and will be released to the environment during personal washing. Approximately 1% of the end product will remain in the empty end-use container, this equates to less than 10 kg of notified polymer annually.

RELEASE OF CHEMICAL FROM DISPOSAL

Empty import and end-use containers, including any residual polymer, will go to either drum reconditioners or landfill. Any spilt and clean-up material will go to landfill. The equipment cleaning effluent, containing any notified polymer, will go to on site treatment plants where the effluent will be treated with flocculants with the resultant solids (containing the majority of the notified polymer present in the washing effluent) going to landfill and the effluent being released to sewer.

7.1.2 Environmental fate

No environmental fate data were submitted.

It is predicted that up to 97% of the notified polymer will be disposed of the sewage for further waste water treatment. The rest of the notified polymer will be disposed of directly to landfill. In the sewer the notified polymer is expected to partially remain in the water compartment based on its hydrophilic structure and relatively high water solubility. The remainder will stick to sludge, which will be disposed of to landfill. The notified polymer in landfill may partially leach and be subject to slow degradation into water and oxides of carbon via biotic and abiotic pathways.

7.1.3 Predicted Environmental Concentration (PEC)

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	21.161	million
Removal within STP	0%	
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.65	µg/L
PEC - Ocean:	0.06	µg/L

A PEC value of 0.65 µg/L to river water has been calculated based on the worst scenario, assuming all the notified polymer be released to aquatic ecosystem.

7.2. Environmental effects assessment

No ecotoxicity data were submitted. Generally, this type of polyanionic polymer will not be toxic to fish or daphnids, with a LC 50 > 100 mg/L. However, anionic polymers are known to be moderately toxic to algae. The mode of toxic action is over-chelation of nutrient elements needed by algae for growth. The highest toxicity is when the acid is on alternating carbons of the polymer backbone, with the 96 h EC50 for green algae ranging from 3.13 to 37.4 mg/L with a geometric mean of 8.6 mg/L. This could apply to notified polymer.

The notified polymer could be toxic to algae based on the above discussion.

7.2.1 Predicted No-Effect Concentration

On basis of the above discussion, assuming the endpoint of the notified polymer to algae is 8.6 mg/L, the resultant Predicted No Effect Concentration (PNEC) is 8.6 µg/L with a conservative assessment factor of 1000.

7.3. Environmental risk assessment

Risk Assessment	PEC µg/L	PNEC µg/L	PEC/PNEC
Q - River	0.65	8.6	0.08
Q - Ocean	0.06	8.6	0.01

The Risk Quotient (PEC/PNEC) to river water has been determined to be 0.08, based on the worst scenario of assuming all the notified polymer is released to the aquatic environment. Therefore, The notified polymer is not considered to pose an unaccepted risk aquatic ecosystem based on predicted low PEC/PNEC.

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified polymer in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1300 kg/m^3). Using these assumptions, irrigation with a

concentration of 0.65 µg/L may potentially result in a soil concentration of approximately 5.0×10^{-3} mg/kg. Assuming accumulation of the notified polymer in soil for 5 and 10 years under repeated irrigation, the concentration of notified polymer in the applied soil in 5 and 10 years may be approximately 2.5×10^{-2} mg/kg and 5.0×10^{-2} mg/kg, respectively.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified polymer cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

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

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

Environmental risk assessment
On the basis of the low volume and the nature, the notified polymer is not considered to pose a risk to the environment.

Recommendations
CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified polymer as introduced:
  - Avoid contact with skin and eyes

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified polymer as introduced:
  - Protective gloves
  - Eye goggles
  - Overalls

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

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

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

Disposal

- The notified polymer should be disposed of to landfill.

Emergency procedures

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

Regulatory Obligations

Secondary Notification

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

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

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

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

No additional secondary notification conditions are stipulated.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Water Solubility 0.35 ± 0.01 g/L at 20 ± 1°C (measured at pH 5) (Tinovis GTC containing approximately 30% of the notified polymer)

Method	OECD TG 105 Water Solubility. EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	Flask Method. Dissolved organic carbon was determined with reference to total carbon and inorganic carbon (standard solutions) calibration curves. In the definitive test, about 50 mL of pure water was added to ~200 mg test dispersion with a solid concentration of 30.4%. The solubility was determined by analysing the concentration of the clear phase from the diluted dispersion, which contained small amounts of undissolved test substance. The water solubility is consistent with the relatively hydrophilic structure of the notified polymer.
Test Facility	IBACON (2008)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Tinovis GTC
METHOD	OECD TG 425 Acute Oral Toxicity: Up-and-Down Procedure.
Species/Strain	Rat/Sprague-Dawley derived, albino
Vehicle	None
Remarks - Method	No deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	175	0
2	1 F	550	0
3	1 F	1750	0
4	3 F	5000	0

LD50	> 5000 mg/kg bw
Signs of Toxicity	For all dose groups tested, all animals survived, gained weight and appeared active and healthy. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour.
Effects in Organs	No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.
Remarks - Results	
CONCLUSION	The test substance is of low toxicity via the oral route.
TEST FACILITY	Product Safety Laboratories (2003a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Tinovis GTC
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/Sprague-Dawley derived, albino
Vehicle	None
Type of dressing	Semi-occlusive.
Remarks - Method	No deviations from the protocol. It is noted OECD TG 425 was quoted for the method in the report.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	5000	0

LD50	> 5000 mg/kg bw
Signs of Toxicity - Local	All animals survived, gained weight and appeared active and health.
Signs of Toxicity - Systemic	There were no signs of gross toxicity, dermal irritation, adverse pharmacological effects or abnormal behaviour.
Effects in Organs	No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.
CONCLUSION	The test substance is of low toxicity via the dermal route.

TEST FACILITY Product Safety Laboratories (2003b)

B.3. Irritation – skin

TEST SUBSTANCE Tinovis GTC

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
- Species/Strain: Rabbit/New Zealand albino
- Number of Animals: 1M, 2F
- Vehicle: None
- Observation Period: 10 days
- Type of Dressing: Semi-occlusive.
- Remarks - Method: No deviations from the protocol. Site cleaned after patch removal.

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	1	1	1	1	7 days	0
Oedema	0	0.3	0	1	24 hours	0

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

Remarks - Results: All animals appeared active and healthy. Apart from the dermal irritation noted below, there were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour.
One hour after patch removal, all three sites exhibited very slight erythema and oedema. The overall incidence and severity of irritation decreases gradually with time. All animals were free of dermal irritation by Day 10 (study termination).
The Primary Dermal Irritation Index is 1.3.

CONCLUSION The test substance is slightly irritating to the skin.

TEST FACILITY Product Safety Laboratories (2003c)

B.4. Irritation – eye

TEST SUBSTANCE Tinovis GTC

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
- Species/Strain: Rabbit/New Zealand albino
- Number of Animals: 1 M, 2 F
- Observation Period: 72 hours
- Remarks - Method: No deviations from the protocol. Fluorescein check at 24 h.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.7	0.7	0.7	2	48 hours	0
Conjunctiva: chemosis	0	0	0.3	1	24 hours	0
Conjunctiva: discharge	0	0	0	1	1 hour	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	-

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

Remarks - Results	All animals appeared active and healthy. Apart from the eye irritation noted below, there were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour. There was no corneal opacity or iritis observed during this study. From one to 48 hours after test substance instillation, all three treated eye exhibited conjunctivitis. All animals were free of ocular irritation by 72 hours (study termination). The Maximum Mean Total Score is 8.0.
CONCLUSION	The test substance is slightly irritating to the eye.
TEST FACILITY	Product Safety Laboratories (2003d)

B.5. Skin sensitisation

TEST SUBSTANCE	Tinovis GTC
METHOD	Analogous to OECD TG 406 Skin Sensitisation - <Magnusson-Kligman>.
Species/Strain	Guinea pig/Hartley albino
Vehicle	Distilled water
PRELIMINARY STUDY	Maximum Non-irritating Concentration: 75% intradermal: 1, 3, 5% topical: 75, 100%
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 5
INDUCTION PHASE	Induction Concentration: intradermal: 5% topical: 100%
Signs of Irritation	Very faint to faint erythema (0.5-1) was noted for all test sites one hour following patch removal for test animals (100% test substance). No irritation was noted at any test site one hour following patch removal for control animals (100% distilled water). Faint to moderate erythema (1-2) was noted at all positive control sites following the topical induction phase for historical positive control animals (85% α-hexylcinnamaldehyde (HCA) as received). Very faint erythema (0.5) was noted at two of five vehicle control sites following the topical induction phase for historical vehicle control animals (100% mineral oil).
CHALLENGE PHASE	
1st challenge	After 20 days topical: 75%
2nd challenge	Not performed
Remarks - Method	No significant variations from the protocol.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*	
		1st challenge	
		24 h	*48 h*
Test Group	75%	0	0
Control Group	75%	0	0
Historical Positive Control Group (hexyl cinnamic acid)	85%	6/10	6/10
Historical Vehicle Control Group (hexyl cinnamic acid)	85%	0	0

Remarks - Results	Test animals (75% w/w mixture of the test substance in distilled water): Very faint erythema (0.5) was noted at five of ten test sites 24 hours following the challenge application. Similar indicators persisted at three sites through 48 hours. Control animals (75% w/w mixture of the test substance in distilled water): Very faint erythema (0.5) was noted at four of five test sites 24 hours following the challenge application. Similar indicators persisted at one site through 48 hours. Historical positive control animals (85% HCA as a 75% w/w mixture in mineral oil): Six of the ten positive control animals exhibited signs of sensitisation response (faint to moderate erythema [1-2]) 24 and 48 hours after challenge patch removal. Very faint erythema (0.5) was noted for three other sites at the 24 and 48 hour interval. Historical vehicle control animals (85% HCA as a 75% w/w mixture in mineral oil): Very faint erythema (0.5) was noted at three of five vehicle control sites 24 and 48 hours after challenge patch removal.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the test substance under the conditions of the test.
TEST FACILITY	Product Safety Laboratories (2003e)

B.6. Skin sensitisation

TEST SUBSTANCE	Tinovis GTC
METHOD	OECD TG 406 Skin Sensitisation - <Magnusson-Kligman>.
Species/Strain	Guinea pig/ Hartley albino
Vehicle	Distilled water
PRELIMINARY STUDY	Maximum Non-irritating Concentration: 75% intradermal: 1, 3, 5% topical: 75, 100%
MAIN STUDY	
Number of Animals	Test Group: 20 Control Group: 10
INDUCTION PHASE	Induction Concentration: intradermal: 5% topical: 100%
Signs of Irritation	Very faint to moderate erythema (0.5-2) was noted at all test sites during the topical induction phase for test animals (100% test substance). Very faint to moderate erythema (0.5-2) was noted at all test sites during the topical induction phase for control animals (100% distilled water). Faint to moderate erythema (1-2) was noted at all positive control sites following the topical induction phase for historical positive control animals (HCA technical as received). Very faint erythema (0.5) was noted at two of five vehicle control sites following the topic induction phase for historical vehicle control animals (100% mineral oil).
CHALLENGE PHASE	
1st challenge	After 23 days topical: 75%
2nd challenge	Not performed
Remarks - Method	No significant variations from the protocol. Twenty-four hours prior to the topical induction, the dose area of each test and control animals were pre-treated with 5% w/w sodium lauryl sulfate (SLS) mixture in petrolatum in order to enhance sensitization by providing a mild inflammatory reaction.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*	
		1st challenge	
		24 h	*48 h*
Test Group	75%	0	0
Control Group	75%	0	0
Historical Positive Control Group (hexyl cinnamic acid)	85%	6/10	6/10
Historical Vehicle Control Group (hexyl cinnamic acid)	85%	0	0

Remarks - Results: Test animals (test substance as a 75% w/w mixture in distilled water): Very faint erythema (0.5) was observed at ten of twenty test sites 24 hours after the challenge dose. Similar irritation persisted through 48 hours.
Control animals (test substance as a 75% w/w mixture in distilled water): Very faint erythema (0.5) was observed at seven of ten test sites 24 hours after the challenge dose. Similar irritation persisted through 48 hours.
Historical positive control animals (HCA technical, as a 75% w/w mixture in mineral oil): Six of the ten positive control animals exhibited signs of sensitisation response (faint to moderate erythema [1-2]) 24 and 48 hours after challenge patch removal. Very faint erythema (0.5) was noted for three other sites at the 24 and 48 hour interval.
Historical vehicle control animals (HCA technical, as a 75% w/w mixture in mineral oil): Very faint erythema (0.5) was noted at three of five vehicle control sites 24 and 48 hours after challenge patch removal.

CONCLUSION: There was no evidence of reactions indicative of skin sensitisation to the test substance under the conditions of the test.

TEST FACILITY: Product Safety Laboratories (2003f)

B.7. Repeat dose toxicity

TEST SUBSTANCE: Tinovis GTC

METHOD: Range finding study to evaluate the overall toxicity associated with oral exposures over a 5-day period.

Species/Strain: Rats/Sprague-Dawley derived, albino
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 5 days
Dose regimen: daily
Post-exposure observation period: 10 days
Vehicle: Distilled water
Remarks - Method: The data from this study will be used, along with existing data, to support dose selections for subsequent toxicity studies.

RESULTS

Dosemg/kg bw/day	*Number and Sex of Animals*	*Mortality*
0	3 per sex	0
200	3 per sex	0
600	3 per sex	0
2000	3 per sex	0

Mortality and Time to Death
All animals survived and appeared active and healthy throughout the study.

Clinical Observations
There were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
In general, and in consideration of variations inherent to a small group size (n =3/sex), body weight body weight gain and total food consumption values of the test groups were comparable to control.

Effects in Organs
No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period. Gross necropsy findings at terminal sacrifice were unremarkable.

CONCLUSION
Based on the conditions of this 5-day test and toxicological endpoints evaluated (which were limited in scope), these results suggest that male and female rats might tolerate a repeated oral high dose exposure of 2000 mg/kg/day in a longer term study.

TEST FACILITY — Product Safety Laboratories (2003g)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE — Tinovis GTC

METHOD — OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA98*, TA100*, TA97a *E. coli*: WP2uvrA (328) *These are also used in the preliminary test.
Metabolic Activation System	An exogenous metabolic activation system (Aroclor® 1254 induced rat liver S9).
Concentration Range in Main Test	a) With metabolic activation: 0, 5, 10, 50, 100, 500, 1000, 2500, 5000 µg/plate b) Without metabolic activation: 0, 5, 10, 50, 100, 500, 1000, 2500, 5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	OECD TG 472 Bacterial Reverse Mutation Test (1997) is not a current OECD TG.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test	> 5000	> 500	> 5000	negative
Present				
Test	> 5000	> 2500	> 5000	negative

Remarks - Results — In the preliminary test, no evidence of substance-related precipitate was observed in all tester strains. Test substance related toxicity, as evidenced by the reduction of the microcolony background lawn and/or as a concentration related reduction in the mean number of revertants per plate, was not observed in any tester strains. No test substance concentration resulted in a mean number of revertants that were 2 times greater than the mean of the concurrent controls in this assay.
In the main test, there was no evidence of substance-related precipitate at any concentration level in this assay. Test substance related toxicity, as evidenced by the reduction of the microcolony background lawn and/or as a concentration related reduction in the mean number of revertants per

	plate, was observed at concentrations at or above 500µg per plate in *S. typhimurium strains* TA97a, TA98, TA100, and TA1535 without exogenous metabolic activation and at 2500 and 5000µg per plate in *S. typhimurium strain* TA97a with the exogenous metabolic activation. No test substance concentration resulted in a mean number of revertants that were 2 times greater than the mean of the concurrent controls in this assay.
CONCLUSION	The test substance was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Next Century Incorporated (2003a) and Next Century Incorporated (2003b)

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