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August 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1,3,5-Triazine, 2,4,6-tris([1,1'-biphenyl]-4-yl)- (INCI Name: Tris-Biphenyl Triazine)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (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 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.

This Public Report is 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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SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1582	BASF Australia Ltd	1,3,5-Triazine, 2,4,6-tris([1,1'-biphenyl]-4-yl)- (INCI Name: Tris-Biphenyl Triazine)	ND	≤ 50 tonnes per annum	Component of cosmetic products

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

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

When used in cosmetic face cream products at ≤ 5% concentration, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of the reported use pattern and expected low hazard to aquatic organisms (based on the non-nanosized notified chemical), the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation:
  - Enclosed, automated processes, where possible
  - Adequate local exhaust ventilation

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation:
  - Avoid contact with skin and eyes
  - Avoid inhalation

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation:
  - Coveralls
  - Impervious gloves
  - Eye protection
  - Respiratory protection, if inhalation exposure may occur

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

- A copy of the (M)SDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, physical 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(1) of the Act; if
- the concentration of the notified chemical exceeds or is intended to exceed 5% in cosmetic face cream products;
- the notified chemical is intended to be used in end-use products applied by spray;
- ecotoxicological studies become available on nanosized notified chemical;

or

(2) 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, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

(Material) Safety Data Sheet

The (M)SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

This notification has been conducted under the cooperative arrangement with the Australian Therapeutic Goods Administration (TGA). The health hazard assessment component of the TGA report was provided to NICNAS and, where appropriate, used in this assessment report. The other elements of the risk assessment and recommendations on safe use of the notified chemical were carried out by NICNAS and the Department of the Environment.

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
BASF Australia Ltd (ABN: 62 008 437 867)
Level 12
28 Freshwater Place
SOUTHBANK VIC 3006

NOTIFICATION CATEGORY
Standard (Reduced fee notification): Ultraviolet filter in a cosmetic to be applied to the skin – Assessed by Comparable Agency.

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: other names, analytical data, degree of purity, identity of manufacturer, import volume and use details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: photostability, carcinogenicity/photocarcinogenicity and potential to interact with other UV filters.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
TGA (2015)

NOTIFICATION IN OTHER COUNTRIES
REACH (2015)
Switzerland (2014)
Philippines

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Tinosorb® A2B

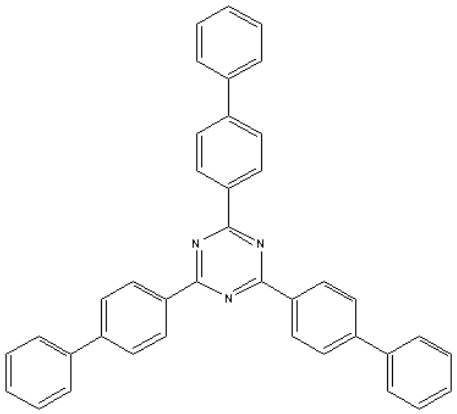
CAS NUMBER
31274-51-8

CHEMICAL NAME
1,3,5-Triazine, 2,4,6-tris([1,1'-biphenyl]-4-yl)-

OTHER NAME(S)
ETH50
C-801
FAT 65'080
FAT 65'080/A
FAT 65'080/B
FAT 65'082/B
Tris-biphenyl triazine (AAN)

MOLECULAR FORMULA
$C_{39}H_{27}N_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
537.66 Da

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

3. COMPOSITION

DEGREE OF PURITY
≥ 98%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Fine, light yellow powder

Property	Value	Data Source/Justification
Melting Point	281.3 °C	Measured
Boiling Point	> 400 °C at 101.3 kPa	Measured
Density	1,256 kg/m^3 at 20 °C	Measured
Vapour Pressure	4.15 x 10^{-24} kPa at 25 °C	Calculated
Water Solubility	< 3 × 10^{-8} g/L at 25 °C	Measured
Hydrolysis as a Function of pH	t½ > 1 year at pH 4, 7, and 9	Measured
Partition Coefficient (n-octanol/water)	Log P_{OW} > 5.6 at 21 °C	Measured
Surface Tension	66.7 mN/m at 20 °C	Measured
Adsorption/Desorption	Log K_{OC} = 4.9	Measured
Dissociation Constant	pKa = -3.1	Calculated
Particle Size	d(0.5)† = 110 ± 16 nm	Measured. Particle size used in product formulations
Specific Surface Area	54.9 m^2/g*	Measured
Flash Point	Not determined	Notified chemical is a solid
Flammability	Not determined	Measured. Notified chemical has no pyrophoric properties and does not liberate flammable gases in contact with water
Autoignition Temperature	Not auto flammable	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidative properties.

† d(0.5) = 50% of particles less than the size specified
* For nanosized notified chemical (87 nm)

DISCUSSION OF PROPERTIES
All physical and chemical properties of the notified chemical (except specific surface area and particle size) were determined on the notified chemical with a particle size of d(0.5) = 15,400 nm. The imported product and finished cosmetic products will contain the notified chemical with a particle size in the range d(0.5) = 110 ± 16 nm. A significant fraction (> 40%) of the notified chemical is therefore expected to be present at the nano-scale (i.e. < 100 nm).

The notified chemical has been shown to be stable in 0.5% carboxymethylcellulose and in the commercial formulation used. A study comparing the stability of the nanosized notified chemical in fresh and stored (eight months) representative commercial formulations indicated that particle agglomeration of the notified chemical was not likely to have occurred in the formulation.

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported into Australia as a component of an aqueous dispersion at < 60% concentration. The notified chemical will be present in the imported product as suspended particles with a significant fraction (> 40%) expected at the nano-scale (i.e. < 100 nm).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	1 - 10	1 – 10	10 – 30	10 – 30	30 - 50

PORT OF ENTRY
Melbourne and Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
BASF Australia Ltd

TRANSPORTATION AND PACKAGING
The notified chemical (at < 60% concentration) will be imported as a component of an aqueous dispersion in 25 kg plastic drums. The notified chemical will be transported from the port of entry to the notifier's chosen facility for storage in its original packaging until transportation to the customer site. End-use products (containing the notified chemical at ≤ 5% concentration) will be packaged in typical consumer-sized containers suitable for retail sale.

USE
The notified chemical will be used as a UVA filter in cosmetic leave-on face cream products at ≤ 5% concentration. A significant fraction (> 40%) of suspended particles of the notified chemical present in the finished cosmetic products is expected to be at the nano-scale (i.e. < 100 nm).

OPERATION DESCRIPTION
No manufacturing, processing, reformulating or repackaging will occur at the notifier's facility. The imported products containing the notified chemical (at < 60% concentration) will be stored at the notifier's facilities until they are transported to customer facilities (in original importation packaging).

At the customer facilities, the procedures for incorporating the notified chemical (at < 60% concentration) into end-use products will likely vary depending on the nature of the cosmetic products formulated, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and occur in a fully enclosed environment followed by automated filling of the reformulated products into containers of various sizes.

End-use products
Cosmetic products containing the notified chemical (at ≤ 5% concentration) may be used by consumers and professionals (such as beauticians). Depending on the nature of the product, application of products could be by hand or through the use of an applicator. Spray application is not expected to occur.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	< 0.5	84
Plant operators	3 - 5	60 - 80
Laboratory	0.5 - 1	30 - 40
Retail workers	8	240

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical as a component of an aqueous dispersion (at < 60% concentration) or in end-use products (≤ 5% concentration), only in the event of accidental rupture of containers.

Reformulation
During reformulation, dermal and ocular exposure of workers to the notified chemical (at < 60% concentration) may occur during weighing and transfer stages, equipment preparation, blending, quality control analysis, and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of automated/enclosed systems and personal protective equipment (PPE) such as gloves, eye protection, and coveralls. Given the particles of the notified chemical are suspended in the imported formulation no inhalation exposure is expected, unless aerosols are formed.

End-use
Exposure to the notified chemical in end-use products (at ≤ 5% concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. workers in beauty salons). Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical. Given the nature of the products, and that no spray application will occur, inhalation exposure is not expected.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical at ≤ 5% concentration through the use of leave-on cosmetic products (face creams). The principal route of exposure will be dermal, while accidental ocular and oral exposure is also possible. Given the nature of the products, and that no spray application will occur, inhalation exposure is not expected.

Data on the typical use pattern of face cream products in which the notified chemical will be used are shown in the following table (SCCS, 2012). For the purposes of the exposure assessment, Australian use patterns are assumed to be similar to those in Europe.

Product type	**Amount** (mg/day)	**C** (%)	**Retention Factor (RF)** (unitless)	**Daily systemic exposure** (mg/kg bw/day)
Face cream	1540	5	1	0.0024

C = concentration of the notified chemical; RF = retention factor.
Daily systemic exposure = (Amount × C × RF × DA)/BW

Using a dermal absorption (DA) of 0.2% for the notified chemical (see Section 6.2, *Toxicokinetics, metabolism and distribution*) and a lifetime average female body weight (BW) of 64 kg (enHealth, 2012), an internal dose of 0.0024 mg/kg bw/day was estimated for the notified chemical for use in cosmetic face cream products.

6.2. Human Health Effects Assessment

As the notified chemical will be present in the finished cosmetic products as suspended particles (d(0.5) = 110 ± 16 nm) with a significant fraction (> 40%) expected at the nano-scale (< 100 nm), studies were provided using batches of nanosized notified chemical (d(0.5) ≤ 120 nm), equivalent to the commercialised material. In addition, studies were also provided for non-nanosized notified chemical (d(0.5) = 440-15,400 nm). The results from the toxicological investigations conducted on the nanosized and non-nanosized notified chemical are summarised in the following table. The studies have been previously assessed by the Australian Therapeutic Goods Administration **(**TGA) and European Scientific Committee on Consumer Safety (SCCS, 2011).

Endpoint	*Particle size (d(0.5))*	*Result and Assessment Conclusion*
Rat, absorption, distribution and excretion	86 nm	0.06% of administered oral dose absorbed; 93.34% of dose excreted unabsorbed with the faeces (48 hours)
Rat, absorption, distribution and excretion	6,140 nm	0.73% of administered oral dose absorbed; 97.2% of dose excreted unabsorbed and unchanged with the faeces (48 hours)
Rat, *in vitro* percutaneous penetration	440 nm	0.12%*
	86 nm	0.02%*
Human, *in vitro* percutaneous penetration	440 nm	0.10%*
	86 nm	0.02%*
Human, *in vitro* percutaneous penetration (pre-damaged skin)	120 nm	0.76%*
Rat, *in vivo* dermal absorption	440 nm	0.11%
Rat, acute oral toxicity	81 nm	LD50 > 1,000 mg/kg bw
	15,400 nm	LD50 > 2,000 mg/kg bw
Rat, acute dermal toxicity	15,400 nm	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	109 nm	LC50 > 0.4976 mg/L/4 hour
Rabbit, skin irritation	15,400 nm	slightly irritating
Rabbit, eye irritation	15,400 nm	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	15,400 nm	inadequate evidence of sensitisation
Guinea pig, phototoxicity and photoallergenicity	15,000 nm	non-phototoxic at 10% non-photoallergenic at 10%
Human, phototoxicity and photoallergenicity	90 nm	non-phototoxic at 9.9% non-photoallergenic at 9.9%
Hairless mice, phototoxicity study – 13 weeks	81 nm	non-phototoxic
Mutagenicity – bacterial reverse mutation	15,400 nm	non mutagenic
Photomutagenicity – bacterial reverse mutation	15,400 nm	non-mutagenic
Genotoxicity – *in vitro* chromosomal aberration test, human lymphocytes	15,400 nm	non genotoxic
Genotoxicity – *in vitro* mammalian mutation test, mouse lymphoma cells	15,400 nm	non-genotoxic
Photomutagenicity – *in vitro* chromosomal aberration test, Chinese Hamster V79 cells	15,400 nm	non-photoclastogenic
Genotoxicity – *in vivo* bone marrow micronucleus test by intraperitoneal route in mice	81 nm	non genotoxic
Genotoxicity – *in vivo* bone marrow micronucleus test by intraperitoneal route in mice	15,400 nm	non genotoxic
Genotoxicity – *in vivo*/*in vitro* unscheduled DNA synthesis assay in rat hepatocytes	81 nm	non genotoxic

Genotoxicity – *in vivo*/*in vitro* unscheduled DNA synthesis assay in rat hepatocytes	15,400 nm	non genotoxic
Rat, repeated dose oral toxicity – 13 weeks	15,400 nm	NOAEL - 1,000 mg/kg bw/day
Rat, repeated dose dermal toxicity – 13 weeks	109 nm	NOAEL – 500 mg/kg bw/day
Rat, reproductive and developmental toxicity	109 nm	NOAEL – 1,000 mg/kg bw/day
Rat, prenatal developmental toxicity	15,400 nm	NOAEL – 1,000 mg/kg bw/day
Rat, androgen receptor binding, *in vitro*	15,400 nm	Does not interact with rat androgen receptor
Rat, oestrogen receptor binding, *in vitro*	15,400 nm	Does not interact with rat estrogen receptor
Rat, uterotrophic assay	15,400 nm	NOEL – 1,000 mg/kg bw/day

* The amount that penetrated the skin (i.e. that was received in the receptor fluid)

Toxicokinetics, metabolism and distribution

Two *in vivo* absorption, distribution and excretion (ADE) studies (in accordance with OECD TG 417) were performed in rats dosed with 100 mg/kg bw ^{14}C-radiolabelled non-nanosized (6,140 nm) or nanosized (86 nm) notified chemical. In both studies, the notified chemical was poorly absorbed from the gastro intestinal (GI) tract (0.73% and 0.06% of administered dose; particle size 6,140 nm and 86 nm, respectively) into the systemic circulation, with 97.2% and 93.34% (particle size 6,140 nm and 86 nm, respectively) of the dose excreted unabsorbed and unchanged with the faeces within 48 hours of exposure. The concentration of radioactivity in blood and plasma plateaued at 1 hour post-exposure (2.463 and 4.359 µg notified chemical equivalents/g and 0.360 µg notified chemical equivalents/g; particle size 6,140 nm and 86 nm, respectively) remaining constant until 8 hours post dosing when levels decreased with a half-life$_{(8 - 48\ h)}$ of about 13 and 31 hours (particle size 6,140 nm and 86 nm, respectively). The highest concentration of ^{14}C-labelled notified chemical for both particle sizes was observed in abdominal fat. For the nanosized notified chemical (86 nm), the concentration of ^{14}C-labelled notified chemical was below the limit of quantification while for the non-nanosized notified chemical (6,140 nm), the concentration was 1.712 µg notified chemical equivalents/g (with all other tissues exhibiting concentrations below 0.110 µg notified chemical equivalents/g).

Two *in vitro* percutaneous penetration studies (in accordance with OECD TG 428) were performed on split-thickness rat and human skin membranes with non-nanosized (440 nm) and nanosized (86 nm) notified chemical. Mean recovery of the applied non-nanosized notified chemical was 95.48% and 91.83% (for rat and human skin, respectively). The majority of the applied dose of the non-nanosized notified chemical was rinsed off from the skin after 24 hours [70.57% (rat) and 73.18% (human)]. The mean amount of non-nanosized notified chemical present in the outer layers of the stratum corneum was 15.97% in rat skin and 15.38% in human skin, with 4.95% and 0.18% in the remaining skin membrane (of rat and human skin, respectively) following tape stripping of the stratum corneum. The mean amount of the non-nanosized notified chemical that penetrated the skin over the study period (i.e. that was received in the receptor fluid) was 0.12% and 0.10 % (rat and human skin, respectively). Overall the mean total absorbed amount of the non-nanosized notified chemical was 5.07% and 0.28% for rat and human skin, respectively.

Mean recovery of the applied nanosized notified chemical was 98.2% and 98.94% (for rat and human skin, respectively). The majority of the applied dose of the nanosized notified chemical was rinsed off from the skin after 24 hours [82.73% (rat) and 94.49% (human)]. The mean amount of nanosized notified chemical present in the outer layers of the stratum corneum was 13.46% in rat skin and 3.73% in human skin, with 1.36% and 0.04% in the remaining skin membrane (of rat and human skin, respectively) following tape stripping of the stratum corneum. The mean amount of the nanosized notified chemical that penetrated through the rat and human skin membranes over the study period (i.e. that was received in the receptor fluid) was 0.02%. Overall the mean total absorbed amount of the nanosized notified chemical was 1.38% and 0.06% for rat and human skin, respectively.

In an *in vitro* percutaneous penetration study (in accordance with OECD TG 428) using pre-damaged split-thickness human skin membranes and nanosized notified chemical (120 nm), the majority of the applied dose of the nanosized notified chemical was rinsed off from the skin after 24 hours (101.14%). The mean amount of nanosized notified chemical present in the outer layers of the stratum corneum was 3.4%, with 0.05% in the remaining skin membrane following tape stripping of the stratum corneum. The mean amount of the nanosized notified chemical that penetrated the skin over the study period (i.e. that was received in the receptor fluid) was 0.76 % of the administered dose.

In an *in vivo* dermal absorption study (in accordance with OECD TG 427) in rats with non-nanosized notified chemical (440 nm), the majority of the applied dose (90-92%) of the radioactively labelled non-nanosized

notified chemical was rinsed off the application site at the end of the 6 hour exposure period, with 2.1-4.4% remaining in/on the treated skin area almost exclusively located in/on the stratum corneum. Less than 0.1% of the dose was found in the lower skin layers (corium and subcutis). After the 6 hour exposure period, only 0.11% of the dose was systemically absorbed with a penetration rate of 0.3345 μg/cm^2/h. During the three days after exposure, the amount of the non-nanosized notified chemical remaining in/on the treated skin after washing led only to a very low increase of the systemic absorption (0.15%). The highest concentration of radioactivity in blood and plasma was found 6 hours after start of exposure, accounting for 0.1272 ppm and 0.2327 ppm notified chemical equivalents, respectively. The residues in liver and kidneys were similar to that observed in blood and plasma.

Dermal absorption for exposure calculations

In the *in vitro* percutaneous penetration study using human skin membranes with nanosized (86 nm) notified chemical, the mean dermal absorption was 0.06%. Given a large variability in absorption values in the study with most of the values below the limit of quantification, the mean ± 2 standard deviations were used in the exposure calculations. This results in a total absorption value for nanosized notified chemical (equivalent to the commercial material) of 0.2% for human skin.

Acute toxicity

In acute oral toxicity studies conducted in rats (in accordance with OECD TG 423), non-nanosized (15,400 nm) and nanosized notified chemical (49.5%; 81 nm) were found to be of low acute toxicity (LD50 > 2,000 mg/kg bw). There were no clinical signs of toxicity, no departure from normal body weight development, no mortalities and no unusual lesions at necropsy.

In an acute dermal toxicity study in rats (in accordance with OECD TG 402), non-nanosized notified chemical (< 15,400 nm) was found to be of low acute toxicity (LD50 > 2,000 mg/kg bw). There were no signs of toxicity or mortality.

In an acute inhalation toxicity study (in accordance with OECD TG 403), no lethality was observed in rats exposed nose-only to an aerosol of nanosized notified chemical (109 nm) at 0.4976 mg/L for 4 hours. Animals exposed to the notified chemical exhibited increases of total cell count (macrophage and neutrophil numbers), TNFα and total protein in bronchoalveolar lavage fluid (BALF), and of absolute and relative lung weight as well as histopathological changes of granulocytic infiltration, diffuse alveolar histiocytosis and alveolar lining cell activation on day 2 of the study. The study authors considered these to be indicative of an inflammatory response representing an acute clearance reaction to the lung burden of the notified chemical. Reversal of the effects was indicated by Day 15 (with only mean lung weight remaining slightly higher in males).

Irritation/Sensitisation

No irritation or sensitisation studies were submitted for nanosized notified chemical.

Non-nanosized notified chemical (15,400 nm) was found to be slightly irritating to the eye and skin. In a skin irritation study (in accordance with OECD TG 404), very slight erythema was observed in one (of one) animal on days 1 and 2 following exposure to the notified chemical for 3 minutes, and one (of three) animals, one hour after a 4 hour exposure period. No other adverse effects were recorded.

In an eye irritation study (in accordance with OECD TG 405), all three animals exhibited very slight or slight chemosis, very slight or slight conjunctival redness and/or a clear discharge over 72 hours. Slight iritis was also observed in one animal on day 1.

In a murine local lymph node assay (LLNA) (in accordance with OECD TG 429), no signs of local irritation or systemic toxicity were observed with non-nanosized notified chemical (15,400 nm). A positive lymphoproliferative response (SI = 3.98) was observed in those animals exposed to the lowest tested concentration (0.5%) of the notified chemical. However, as no positive response or dose-response relationship was observed in the higher tested concentrations (1%, 2.5%, 5% and 10%) this response was not considered biologically relevant by the study authors. Therefore, no lymphoproliferative response was attributed to delayed contact hypersensitivity as a result of exposure to the notified chemical.

Phototoxicity and Photoallergenicity

Non-nanosized notified chemical (15,000 nm) did not induce a phototoxic or photoallergenic response in guinea pigs at 10% concentration where animals were exposed to UVA and UVB radiation at wavelengths of 365 nm and 312 nm, respectively.

Nanosized notified chemical (90 nm) did not induce a phototoxic or photoallergenic response in humans where 53 subjects were exposed to six cycles of application and irradiation (UVA/UVB light) to a cream formulation containing the notified chemical at 9.9% concentration. Sixteen adverse reactions were reported in thirteen subjects. One subject reported skin peeling and itching at the control site over three days which stopped when UV irradiation of the control site was stopped. The study's authors attributed itching at the test site in seven subjects to the tape used to secure the test patches. All adverse effects were resolved before completion of the study.

In a 13 week dermal toxicity study, hairless mice were exposed to nanosized notified chemical (81 nm) at dose levels of 80, 160, 325 and 650 mg/kg bw/day of the notified chemical and were exposed to UV light (5 days per week for 13 weeks). No treatment related effects on body weight, or increase in oedema formation, wrinkling or skin fold thickness were observed compared to control animals.

Repeated dose toxicity
In a 13-week repeated dose oral (gavage) toxicity study followed by a 4-week recovery period (similar to OECD TG 408) in rats exposed to non-nanosized notified chemical (15,400 nm), the NOAEL was established as 1000 mg/kg bw/day based on the absence of adverse effects.

In a 13-week repeated dermal toxicity study followed by a 2-week recovery period (similar to OECD TG 413) in rats exposed to nanosized notified chemical (109 nm), the NOAEL was established as 500 mg/kg bw/day based on a decrease in body weight gain at the highest dose (1000 mg/kg bw/day). Scabs, vocalisation and hyperactivity were also observed at the highest dose. The notified chemical was detected in the blood at low levels (around the level of quantification) of all treated groups (dose levels: 150, 500 and 1,000 mg/kg bw/day) indicating dermal and/or oral absorption (through licking), although there was no dose response. Since low levels were still present two weeks after the end of exposure, the possibility exists for accumulation of the notified chemical.

Mutagenicity/Genotoxicity/Photomutagenicity
Genotoxicity was examined *in vitro* in bacterial and mammalian cell systems, as well as *in vivo* in rats and mice. All *in vitro* genotoxicity studies were performed with non-nanosized notified chemical (< 15,400 nm), whereas both *in vivo* studies were performed with non-nanosized and nanosized particles (~80 nm).

In vitro testing included reverse mutation assays in *S. typhimurium* and *E. coli*, mouse thymidine kinase locus gene mutation assay, chromosomal aberration assays in Chinese Hamster V79 cells (including irradiation) and in cultured human lymphocytes, and a photomutagenicity assay in *S. typhimurium* (reverse mutation). In all these tests there was no evidence that the notified chemical was genotoxic.

An unscheduled DNA synthesis test in rat hepatocytes and an *in vivo* bone marrow micronucleus assay using nanosized (81 nm) and non-nanosized (15,400 nm) notified chemical did not show genotoxicity. Given the low oral absorption and dosing via gavage, it is not clear whether in the UDS test the cells were adequately exposed. However, in the *in vivo* mouse bone marrow assay blood samples showed measurable concentrations of the notified chemical (both in the nano and non-nano groups) indicating that the bone marrow had been exposed to the test item. It is worth noting that in these mice, the only clinical findings were piloerection and hypoactivity at intraperitoneal exposure doses of 1000 mg/kg (nanosized) and 2000 mg/kg (non-nanosized).

Since the *in vitro* studies were conducted in the presence of metabolic activation and the *in vivo* genotoxicity studies were negative, the potential for the formation of active metabolites has been addressed. Overall the data indicate no concern with regard to potential genotoxicity of the notified chemical.

Toxicity for reproduction
No adverse effects were observed in male and female rats in a combined repeated dose toxicity study and reproduction/developmental toxicity screening test (in accordance with OECD TG 422) with nanosized notified chemical (109 nm). In the study, animals were exposed to the notified chemical at doses of 0, 100, 500 or 1000 mg/kg bw/day for two weeks before mating, during mating, gestation and to day 4 *post-partum* for females. No adverse clinical effects or mortality were related to exposure to the test substance, including no adverse effects on oestrous cycling, pairing, mating or fertility. Two of ten females in the high-dose group exhibited aggregates of large histocytes in the bronchioles. However, the study's authors attributed this effect to accidental aspiration during oral gavage and not to exposure to the test substance. The NOAEL was considered to be 1,000 mg/kg bw/day based on the absence of adverse effects.

No adverse effects were observed in a prenatal developmental study in rats (in accordance with OECD TG 414) with non-nanosized notified chemical (15,400 nm). In the study, animals were exposed to the notified chemical by oral gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day from day 6 to day 19 *post coitum*. No signs of maternal toxicity were observed. One of 282 foetuses from the high-dose group exhibited mandibular micrognathia associated with microglossia as well as markedly dilated cerebral ventricles. However, as this effect was not observed in other foetuses, the study authors did not consider it to be related to exposure to the notified chemical. No increase in skeletal malformations or variations were observed. Based on the absence of treatment-related adverse effects, the NOEL was determined to be 1,000 mg/kg bw/day.

Endocrine effects
In an *in vitro* oestrogen binding assay and an *in vitro* androgen receptor binding assay, non-nanosized notified chemical (15,400 nm) did not displace oestradiol from cytosolic preparations of rat uterine tissue (from 40 immature females) or ^{3}H-R1881 from cytosolic preparations of rat prostate gland tissue (8 males) indicating that the non-nanosized form of the notified chemical did not possess intrinsic potential to interact with the rat androgen or oestrogen receptors.

In an uterotrophic assay in immature female rats, female rats were dosed with 0, 250, 500 or 1000 mg/kg bw/day non-nanosized notified chemical (15,400 nm) by oral gavage for three days. Three animals died during the study (one animal in both the mid- and high dose groups on day 2 and one animal in the high-dose group on day 3). On necroscopy, the deaths were attributed to the oral gavage procedure rather than exposure to the notified chemical. No other adverse effects or clinical signs of toxicity were observed, and no evidence of an uterotrophic response to the notified chemical at doses up to 1000 mg/kg bw/day was observed.

Carcinogenicity
No carcinogenicity studies were provided. However, based on the absence of structural alerts and genotoxicity, and no concerns in the repeated dose toxicity studies, the likelihood of the notified chemical being carcinogenic may be considered to be low.

Interaction with other UV filters
No data on the possible interaction of the notified chemical with other UV filters likely to be found in cosmetic products were provided. However, the notified chemical (nanosized) was shown to be stable under conditions of changing storage tests at different temperature and humidity over periods of 6 months (40 ^{o}C/ 75% relative humidity) and 24 months (25 ^{o}C/ 60% relative humidity), and a comparative absorbance spectra for a sample after 8 months' storage at room temperature for a newly prepared formulation (containing the notified chemical at $\leq$ 10% concentration) showed the shape of each UV absorption spectrum to be similar. In the human phototoxicity and photoallergenicity test, no significant differences of active content of the notified chemical (non-nanosized) in a sunscreen formulation were found without irradiation and after irradiation with 3 MED (minimal erythema dose). Therefore, lack of specific interaction data with other UV filters could be justified by the stable (and photostable) nature of the notified chemical.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Characterisation
A significant fraction (> 40%) of the particles of the notified chemical (d(0.5) = 110 ± 16 nm) present in the imported and finished cosmetic products is expected to be at the nano-scale (< 100 nm). All endpoints, except for acute dermal toxicity, skin and eye irritation, and sensitisation (which were conducted using non-nanosized notified chemical), were conducted using nanosized notified chemical (d(0.5) $\leq$ 120 nm), equivalent to the commercialised material. Given the very limited systemic exposure, no indication of irritation in the repeated dose dermal toxicity study with nanosized notified chemical and there were no signs of irritation and photoallergenicity in the human study, the results of the studies conducted with non-nanosized notified chemical is considered acceptable to estimate the toxicity of nanosized notified chemical.

Absorption by the oral and dermal routes of the non-nanosized and nanosized notified chemical is low (i.e. around the levels of quantification). No systemic effects were observed after oral or dermal exposure up to 500 mg/kg bw/day.

Based on the available information, the notified chemical is generally of low toxicity, presenting only as a slight skin and eye irritant. However, in an acute inhalation toxicity study with nanosized notified chemical, a strong inflammatory response was seen in the lung of exposed animals after 4 hours that was not completely resolved after 15 days. Given the lack of a repeated dose inhalation toxicity study, the effects from repeated exposure to the notified chemical at lower doses via inhalation for a longer duration are not known.

In the repeated dose dermal toxicity study with nanosized notified chemical, low levels of the notified chemical were still present two weeks after the end of exposure, indicating the possibility for accumulation of the notified chemical. However, given the very low levels (around the limit of quantification), and the exaggerated exposure scenario, this is not considered a concern for the notified chemical under the proposed use scenario.

6.3.1. Occupational Health and Safety

Reformulation

During reformulation, workers may be at risk of slight eye and skin irritation effects when handling the notified chemical as introduced at < 60% concentration. The potential risk of toxic effects from inhalation exposure to the notified chemical if aerosols are formed can also not be ruled out. However, these risks should be reduced through the control measures in place to minimise worker exposure, including the use of enclosed, automated processes and PPE. Therefore, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use

Beauty care professionals will handle the notified chemical at ≤ 5% concentration, similar to public use. Therefore the risk to workers who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment see Section 6.3.2.

6.3.2. Public Health

Local toxicity

The notified chemical has the potential to cause slight eye and skin irritation. However, irritation effects are not expected from use of the notified chemical at the proposed use concentrations (≤ 5%) in cosmetic face cream products.

Systemic toxicity

Members of the public may experience repeated exposure to the notified chemical through the use of cosmetic face cream products containing the notified chemical (at ≤ 5% concentration). The principal route of exposure will be dermal, while accidental ocular and oral exposure is also possible.

The repeat dose toxicity potential of the notified chemical was estimated by calculation of the margin of exposure (MoE) of the notified chemical using an estimated internal dose of 0.0024 mg/kg bw/day (see Section 6.1.2), a dermal absorption value of 0.2% and the NOAEL of 500 mg/kg bw/day, as determined in a 28-day repeated dose dermal toxicity study on nanosized notified chemical (109 nm). Using the abovementioned NOAEL, a MoE of 208,333 was estimated. A MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure; therefore, the MoE is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 5% concentration in cosmetic face cream products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of an aqueous dispersion for reformulation into finished cosmetic products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the product containing the notified chemical is expected to be collected with adsorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve manual transfer of the raw material containing the notified chemical into blending vessels. Blending operations will be highly automated, and are expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemical from this process to the environment is not expected. The process will be followed by automated filling of the formulated products into end-use containers of various sizes. Wastes containing the notified chemical generated during reformulation include equipment wash water, spilt materials, and empty import containers. Wastes may be collected and released to sewers in a worst case scenario, or disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemical is expected to be released to sewer across Australia as a result of its use in various cosmetic products, which will be washed off the skin of consumers and disposed of to the sewer. A small proportion of the notified chemical is expected to be disposed of to landfill as residue in empty end-use containers.

RELEASE OF CHEMICAL FROM DISPOSAL

A small proportion of the notified chemical may remain in end-use containers once the consumer products are used up. Residues of the notified chemical remaining in the empty containers are likely to share the fate of the container and be disposed of to landfill, or to be released to sewer when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic formulations, the majority of the notified chemical is expected to enter the sewer system, before potential release to surface waters nationwide. Based on the results of a biodegradability study on non-nanosized notified chemical, it is not considered to be readily biodegradable (7% in 28 days). For details of the environmental fate study, please refer to Appendix B. Based on its low molecular weight and high partition coefficient (log P_{OW} > 5.6), the notified chemical has the potential to bioaccumulate. However, based on its low water solubility and high adsorption coefficient (log K_{OC} = 4.9), the notified chemical is expected to bind to sludge and sediment. As such, during sewage treatment plant (STP) processes the majority of the notified chemical is expected to be removed in sewage sludge, and is therefore unlikely to be released to supernatant waters at ecotoxicologically significant concentrations. In surface waters, the notified chemical is expected to adsorb to soil and sediment, and eventually degrade through biotic and abiotic processes to form water and oxides of carbon and nitrogen.

The majority of the notified chemical will be released to sewer after use. A proportion of the notified chemical may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation. A proportion of the notified chemical may also be disposed of to landfill as collected spills and empty container residue. The notified chemical residues in landfill, soil and sludge are expected to eventually degrade to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal in the STPs.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	50,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	50,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	136.99	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	30.29	µg/L

PEC - Ocean:	3.029 µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 30.29 µg/L may potentially result in a soil concentration of approximately 201.9 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 1.010 mg/kg and 2.019 mg/kg, respectively. Following water treatment processes, the notified chemical is expected to aggregate and form larger particle sizes, no longer in the nanosize range (see Section 7.3, Environmental Risk Assessment).

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on non-nanosized notified chemical (15,400 nm) in accordance with OECD test guidelines are summarised in the table below. Details of these studies can be found in Appendix B. The notified chemical released to sewer from use is expected to form aggregates during water treatment processes, and is not expected to be released to the environment with particle sizes in the nanosize range. As such, the results of ecotoxicological studies on the non-nanosized notified chemical are considered to be a reasonable estimation of the ecotoxicity of the notified chemical in cosmetic formulations.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LL50 > 100 mg/L (WAF*)	Not harmful to fish up to water solubility limit
Daphnia Toxicity	48 h EL50 > 100 mg/L (WAF*)	Not harmful to aquatic invertebrates up to water solubility limit
Daphnia Chronic study	21 d NOEC ≥ 0.002 mg/L	Not harmful to aquatic invertebrates up to water solubility limit (chronic)
Algal Toxicity	72 h EL50 > 100 mg/L (WAF*)	Not harmful to algae up to water solubility limit
Inhibition of Bacterial Respiration#	3 h IC50 > 100 mg/L	Not inhibitory to microbial respiration

* Water Accommodated Fraction
# Full study report not available

Based on the above ecotoxicological endpoints, non-nanosized notified chemical is not expected to be harmful to aquatic life up to the limit of its solubility in water. Therefore, the notified chemical is not formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated since the notified chemical is not considered to be harmful to aquatic organisms up to the limit of its solubility in water.

7.3. Environmental Risk Assessment

Ecotoxicological studies were conducted on the notified chemical with a particle size of d(0.5) = 15,400 nm only. No studies were conducted on the notified chemical in the size range as expected in end-use cosmetic products (d(0.5) = 110 ± 16 nm), where a significant fraction of particles at the nano-scale is expected. Given no studies were conducted with nanosized notified chemical, there is uncertainty if the results of the studies adequately reflect the notified chemical as intended to be used in cosmetic products. However, where the notified chemical is released to the sewer it will be subjected to water treatment processes including flocculation. Following flocculation, the notified chemical is expected to form aggregates and the notified chemical is not expected to be released to the environment with particle sizes in the nanosize range. As the notified chemical is expected to be released to the environment as a larger particle size (following water treatment processes), studies on non-nanosized notified chemical were considered to provide a reasonable approximation of the potential for toxicity of the notified chemical in end-use products in the environment. Furthermore, the majority of the notified chemical released to sewer during use in cosmetic formulations is expected to be removed during STP processes, and is unlikely to reach ecotoxicologically significant concentrations.

The Risk Quotient (Q = PEC/PNEC) of the notified chemical has not been calculated as a PNEC is not available. Although the notified chemical is not readily biodegradable, it is not expected to be harmful to aquatic life up to the limit of its water solubility.

Therefore, on the basis of its expected low hazard to aquatic organisms, maximum annual importation volume and assessed use pattern in cosmetic formulations, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 281.3 °C

Method OECD TG 102 Melting Point/Melting Range.
Remarks Differential Scanning Calorimeter
Test Facility RCC (2005a)

Boiling Point > 400 °C

Method OECD TG 103 Boiling Point.
Remarks Differential Scanning Calorimeter. No endothermic peaks detected to indicate boiling.
Test Facility RCC (2005a)

Water Solubility < 0.03 x 10^{-6} g/L at 20 °C

Method OECD TG 105 Water Solubility.
Remarks Column Elution Method
Test Facility RCC (2005b)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$ <hours or days>*
4	50	> 5 days
7	50	> 5 days
9	50	> 5 days

Remarks Notified chemical was stable.
Test Facility RCC (2005c)

Partition Coefficient (n-octanol/water) log Pow = > 5.6 at 21 °C

Method OECD TG 107 Partition Coefficient (n-octanol/water): Shake Flask Method
OECD TG 117 Partition Coefficient (n-octanol/water): HPLC Method
Remarks The HPLC and shake flask methods could not be applied. The Log P_{ow}-value was estimated based on its solubility in n-octanol and in water. When calculated by model calculation, the Log P_{ow}-value was 10.4.
Test Facility RCC (2005a)

Adsorption/Desorption log K_{oc} = 4.9 at 20 °C

Method ISO/DIS 18749, ISO/TC 147/SC 5

Test item	*Concentration in water (%)*	*Concentration in sludge (%)*	*Mean Koc (mL/g)*
1	0.013	1050	75240
2	0.015	1064	

Remarks Test performed in activated sludge at a pH of 6.5 - 7.0. Test substance stable in aqueous solutions. Adsorption of the test substance was up to 98% of the amount applied after 21 hr.
Test Facility RCC (2005d)

Particle Size d(0.5) = 110 ± 16 nm

Method In-house method
Remarks The particle size of a production sample used in the finished cosmetic formulations was characterised using Fiber Optic Quasi Elastic Light Scattering (FOQELS), Transmission

Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM).

Particle size distribution ranged from ~50-380 nm with an estimated > 40% with a particle size at the nano-scale (< 100 nm)

Test Facility Ciba (2007)

Flammability Not highly flammable

Method EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks Notified chemical could not be ignited with a flame during the preliminary test. No further testing required.
Test Facility RCC (2005e)

Autoignition Temperature Not auto-flammable

Method EC Council Regulation No 440/2008 A.16 Relative Self-Ignition Temperature for Solids.
Remarks No exothermic reaction observed.
Test Facility RCC (2005f)

APPENDIX B: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OCED TG 302 C Inherent Biodegradability: Modified MITI-Test (II)
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biological Oxygen Demand (BOD)
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Toxicity control*		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*	*Day*	*% Degradation*
7	2-3	7	35-38	7	72
14	3-5	14	39-42	14	70
21	3-6	21	42-45	21	69
28	6-8	28	43-47	28	73

Remarks – Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 60% by 3 days (64%), and attained 73% degradation in 28 days. Therefore, the tests indicate the suitability of the inoculum. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 2 days (29%; 43-47% in 28 days), showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance after 28 days was a mean of 7%. Therefore, the test substance is not considered to be readily biodegradable according to the OECD (302 C) guideline.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	RCC (2005g)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static.
Species	*Brachydanio rerio* (zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	108 mg $CaCO_3$/L
Analytical Monitoring	Not specified
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. The test substance was prepared as a water accommodated fraction (WAF) due to its low water solubility. A stock solution with a nominal loading rate of 100 mg/L was prepared by ultrasonic treatment of the test substance in water for 15 min followed by intense stirring for 72 hours. Any undissolved material was removed by membrane filtration.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
100	0.0064	7	0	0	0	0	0

LL50	> 100 mg/L at 96 hours (WAF)
NOEL	100 mg/L at 96 hours (WAF)
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 96 h test period. The actual concentrations of the test substance were measured at the start and end of the 96 h test period. As the measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 96 h LL50 and NOEL for fish were determined to be > 100 mg/L and 100 mg/L (WAF), respectively, based on nominal concentrations.

CONCLUSION	The notified chemical is not considered to be harmful to fish up to the limit of its water solubility.
TEST FACILITY	RCC (2005h)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Not specified
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. The test substance was prepared as a water accommodated fraction (WAF) due to its low water solubility. A stock solution with a nominal loading rate of 100 mg/L was prepared by ultrasonic treatment of the test substance in water for 15 min followed by intense stirring for 72 hours. Any undissolved material was removed by membrane filtration.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
100	0.0003	20	0	0

EL50	> 100 mg/L at 48 hours (WAF)
NOEL	100 mg/L at 48 hours (WAF)
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 48 h test period. The actual concentrations of the test substance were measured at the start and end of the 48 h test period. As the measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 48 h EL50 and NOEL for daphnids were determined to be > 100 mg/L and 100 mg/L (WAF), respectively, based on nominal concentrations.

CONCLUSION	The notified chemical is not considered to be harmful to aquatic invertebrates up to the limit of its water solubility.
TEST FACILITY	RCC (2005i)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 211, *Daphnia magna* Reproduction Test – Semi-static.
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	N-N-Dimethylformamide (DMF)
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC, TLC
Remarks - Method	The definitive test was conducted at the nominal concentrations of 0.00013, 0.00025, 0.0005, 0.001, and 0.002 mg/L of the test substance. A total of 20 daphnids were used. The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

	Test Concentration (nominal; mg/L)						
	Control	Solvent control	0.00013	0.00025	0.0005	0.001	0.002
Survival (% of control)	100	97.2	105.3	104.3	100.7	104.2	101.7
Total no. offspring released by survived *Daphnia*	109.4	112.6	118.6	117.4	113.4	117.3	114.6
± SD	6.3	7.7	7.8	12	6.7	14.8	8.8

SD = Standard Deviation

21 day NOEC	> 0.002 mg/L
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were renewed every three days from Day 2 during the 21 d test period. The actual concentrations of the test substance were measured at the start and end of the 21 d test period. As the measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. No significant differences in adult survival and reproduction were observed up to 0.002 mg/L concentration of the test substance. The 21 day NOEC was determined to be > 0.002 mg/L, based on nominal concentrations.
CONCLUSION	The notified chemical is not harmful to aquatic invertebrates on a chronic basis up to the limit of its water solubility.
TEST FACILITY	RCC (2007)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201, Freshwater Alga and Cyanobacteria, Growth Inhibition Test.
Species	*Scenedesmus subspicatus* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L Actual: 0.001-0.0018 mg/L
Auxiliary Solvent	None

Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	Not Specified
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. The test substance was prepared as a water accommodated fraction (WAF) due to its low water solubility. A stock solution with a nominal loading rate of 100 mg/L was prepared by ultrasonic treatment of the test substance in water for 15 min followed by intense stirring for 72 hours. Any undissolved material was removed by membrane filtration.

RESULTS

Biomass		*Growth*	
E_bL50	*NOEL*	*E_rL50*	*NOEL*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
> 100	100	> 100	100

Remarks - Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 72 h test period. The actual concentrations of the test substance were measured at the start and end of the 72 h test period. As the measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 72 h EL50 and NOEL were determined to be > 100 mg/L and 100 mg/L (WAF), respectively, based on nominal concentrations.

CONCLUSION	The notified chemical is not considered to be harmful to algae up to the limit of its water solubility.
TEST FACILITY	RCC (2005j)

C.2.5. Acute toxicity to terrestrial invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 207, Earthworm, Acute Toxicity Tests.
Species	*Eisenia fetida* (earthworm)
Exposure Period	14 days
Auxiliary Solvent	None
Remarks - Method	The definitive test was conducted at the nominal concentrations of 100, 180, 320, 560, and 1,000 mg/kg dry weight of soil (dry wt) of the test substance. Due to the low solubility of the test substance in water, acetone, dichloromethane, and tetrahydrofurane, the test substance was therefore mixed directly into sand before addition to the artificial testing soil. A total of 40 adult worms were used. The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

	Nominal Test Concentration (mg/kg dry wt)					
	Control	100	180	320	560	1,000
Mortality (%)	0	0	0	0	0	0
Decrease in body weight (%)	3	3	4	1	3	1

LC50	> 1,000 mg/kg (dry wt) at 14 days
NOEC	1,000 mg/kg (dry wt) at 14 days
Remarks - Results	All validity criteria for the test were satisfied. The actual concentrations of the test substance were not measured during the 14 d test period. No significant mortality effects or behavioural abnormalities were observed.

	The 14 d LC50 and NOEC were determined to be > 1,000 mg/kg (dry wt) and 1,000 mg/kg (dry wt), respectively, based on nominal concentrations.
CONCLUSION	The notified chemical is not considered to be harmful to terrestrial invertebrates.
TEST FACILITY	RCC (2005k)

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