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23 April 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

FULL PUBLIC REPORT

TAP

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Director
Chemicals Notification and Assessment

FULL PUBLIC REPORT

TAP

1. APPLICANT

Schwarzkopf Pty Ltd of 20 Rodborough Road, FRENCHS FOREST NSW 2086 has submitted a limited notification statement in support of their application for an assessment certificate for TAP.

2. IDENTITY OF THE CHEMICAL

The chemical name, CAS number, molecular and structural formulae, molecular weight and spectral data, have been exempted from publication in the Full Public Report and the Summary Report.

Marketing Name: TAP

3. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa:	Pale yellow crystals
Boiling Point:	>218°C
Specific Gravity:	Approximately 1 (finished product)
Particle size:	Not relevant (imported in aqueous based formulation)
Vapour Pressure:	2.4kPa at 20ºC (water in finished product)
Water Solubility:	infinitely soluble (ACD software)
Partition Co-efficient (n-octanol/water):	log P -0.96 (ACD software)
Hydrolysis as a Function of pH:	Not relevant (see comments below)
Adsorption/Desorption:	7.17 (ACD software)

Dissociation Constant:	pK_a 3.0-7.0 for 2-amino-pyrimidinium ion pK_a 1.0-5.0 for Arylaminium ion
Flash Point:	Not applicable
Flammability Limits:	Not flammable
Autoignition Temperature:	Not expected to undergo auto-ignition
Explosive Properties:	Not explosive
Reactivity/Stability:	Stable under ambient conditions

Comments on Physico-Chemical Properties

The values for water solubility, partition coefficient, adsorption and dissociation constant were estimated by the notifier via the use of software package developed by Advanced Chemistry Development Inc. (ACD), which is accepted for this assessment.

No hydrolysis value was provided by the notifier because the chemical has no groups that will hydrolyse. The assessment has accepted this reasoning.

The estimated low partition coefficient and adsorption values indicate that the chemical will be highly mobile in soil and likely to remain in the water column.

The pK_a's provided indicate that the chemical is likely to dissociate at the lower end of the environmental pH range.

Values given by the ACD software were compared for this assessment with values obtained using the USEPA ASTER estimation model. The ASTER results for the physico-chemical parameters are shown below. The ACD estimations for water solubility, partition coefficient and adsorption are within acceptable agreement with the ASTER values.

ASTER Generated Physico-Chemical Parameters for $C_4H_8N_6$

Vapour pressure	3.47 X 10^{-3} mm of Hg
Water solubility	3.99 X 10^6 g/L
Partition Coefficient	-0.540 (log P)
Adsorption	1.04 (log K_{oc})
Hydrolysis	unlikely
Dissociation (pKa)	not available

PURITY OF THE CHEMICAL

Degree of Purity:	>99.7%
Hazardous Impurities:	None
Non-hazardous Impurities (> 1% by weight):	None
Additives/Adjuvants:	None

5. USE, VOLUME AND FORMULATION

The notified chemical functions as a precursor (developer) in an oxidation hair dye. It will not be manufactured in Australia but will be imported as a component of water based finished hair colouring product at 2.8% w/w. Import volumes of the notified chemical are 400 kg per annum for the next 5 years in finished 50 mL retail bottles. The hair dye product will be sold through retail outlets for home use.

A near identical chemical to the notified chemical has been in use in Australia by the notifier from March 1996 to March 1999 under a NICNAS Low Volume Chemical permit granted under section 21U of the Act.

6. OCCUPATIONAL EXPOSURE

Transport, Storage and Retail: 1-2 hours/day, 10-15 days/year
Imported retail packs will be transported from the dockside to the notifier's warehouse for storage prior to distribution to retail outlets. At the dockside, one to two workers are expected to be involved in handling the imported packs; one or two transport drivers and two to four warehouse workers will be involved in delivery to and storage at the warehouse.

It is anticipated that the imported hair dye containing the notified chemical will be widely distributed around Australia and approximately 1 000 supermarket workers will handle the bottled product.

Waterside workers, transport drivers, warehouse and supermarket or retail outlet workers should only be exposed in the event of a spill. The notifier indicated that transport and warehouse workers are required to wear overalls and safety boots.

7. PUBLIC EXPOSURE

Public exposure is likely to be intermittent but widespread, with the extent of the population exposed limited only by the commercial success of the product. Hair color is usually applied every 4 to 6 weeks as new growth becomes visible at the base of the hair, thus frequency of exposure is low. The duration of exposure will be approximately 20-30 minutes, following which the color preparation is washed from the hair.

In the event of a transport accident, the extent of a spill will be limited by the small pack size of the product (50 mL). Given the cream based nature of the formulation, dispersion would be minimal and significant public exposure from this source is unlikely. Any spillage would be readily recoverable on adsorbant material with the residue being washed to the drain.

8. ENVIRONMENTAL EXPOSURE

Release

Spills may occur while the hair dye is stored at the warehouse. The notifier has estimated that up to 1% of the imported volume (ie 4 kg of notified chemical per year) may be lost in this way.

Approximately 3% of the product will remain in the bottle after it has been emptied. This equates to 12 kg per year of waste notified chemical in the bottle residue. The empty bottle (including the residue) will be disposed of with the domestic rubbish and subsequently disposed of to landfill or by incineration.

The notifier claims that at least 50% of the dye will absorb to the hair, so annually 200 kg of notified chemical may be released to sewer. When mixed in the appropriate proportions in the dye preparation and applied, the notified chemical should be totally consumed. Thus, no pure notified chemical, and only a proportion of the final dye will enter the sewer.

Fate

A summary of the estimated annual amount of notified chemical wastes is:

Spills	1%	4.0 kg
User container residue	3%	12.0 kg
Total Annual Waste		16.0 kg

Thus, approximately 3% of the imported chemical will end up in landfill or be incinerated. Because of its low partition coefficient and adsorption value, the chemical is likely to be highly mobile in soil and will readily partition to water. Thus, unreacted chemical is likely to leach out of a landfill but in very low concentrations and in a diffuse manner.

The estimated environmental partitioning calculated by the ASTER model for pyrimidine free base indicated it will partition 100% into water.

The biodegradation oxygen demand estimated by ASTER is 2 to 15 days, suggesting that the chemical will readily degrade.

The bioconcentration factor estimated by ASTER is one, indicating that the chemical is unlikely to bioconcentrate

9. EVALUATION OF TOXICOLOGICAL DATA

The notifier has submitted translated summary data on a number of studies carried out the notified chemical. Investigations on the toxicity of hair dye formulations containing the notified chemical at varying concentrations were also conducted to simulate end use conditions.

Summary of the acute toxicity of TAP or TAP in hair dye formulation

Test	*Species*	*Outcome*	*Reference*
Acute oral toxicity:			
100% TAP	Mouse	LD_{50} = 4 700 mg/kg bw	(Potokar 1982b)
1.6% TAP in hair dye; 4.2% TAP in hair dye	Rat	LD_{50} > 5 000 mg/kg bw	(Kastner 1982a)
Skin Irritation:			
Single application			
10% TAP	Rabbit	Slightly irritating	(Potokar 1982c)
1.6% TAP in hair dye	Rabbit	Slightly irritating	(Kastner 1982c)
4.2% TAP in hair dye	Rabbit	Non irritating	(Kastner 1982d)
10% TAP	Human	Non irritating	
Repeat application:			
100% TAP	Mouse	Non irritating	(Potokar 1982d)
10% TAP	Mouse	Non irritating	(Kastner 1983a)
10% TAP	Rabbit	Non irritating	(Potokar 1983b)
10% TAP	Human	Non irritating	(Potokar 1983c)
Eye irritation:			
5% TAP	Rabbit	Slightly irritating	(Potokar 1982e)
1.6% TAP in hair dye	Rabbit	Slightly irritating	(Kastner 1982e)
Skin sensitisation:			
5% TAP*	Guineapig	Non-sensitising	(Potokar 1982e)
<0.1% TAP* in hair dye	Guineapig	Non-sensitising	(Kastner 1982f, 1983b)

* challenge concentration

9.1 Toxicokinetics – Absorption, Distribution and Excretion (Bartnik and Zimmermann 1985) (Bartnik 1988a) (Bartnik 1988b)

Species/strain:	Rat/Wistar (SPF-Cpb): Group I; Rat/Wistar (SPF-TNO): Groups II-V
Number/sex of animals:	Group I: 5/sex; Group II: 8/sex; Group III: 17/sex; Group IV: 8/sex; Group V: 8/sex

Test Material:
Group I: For cutaneous application, the formulation consisted of ^{14}C-labelled test substance (0.451%) mixed with unlabelled test substance, sodium sulfite and ammonium sulfate, basic emulsion Bth 66 B (a mix of fatty alcohols and fatty alcohol polyglycol sulfate), water and ammonia. This was then diluted 1:1 with CO_2-minimized water.

Group II: as described for Group I, except that 2,7-dihydroxynaphthalene (a coupler) was added to the formulation, which was then diluted with 6% aqueous H_2O_2 (to mimic the hair dye product as applied). The concentration of test substance after dilution was 0.117%.

Group III: as described for Group I, except that the formulation was tested with (form 1) or without (form 2) 2-methylresorcinol (a coupler), then diluted with 6% aqueous H_2O_2 (to mimic the hair product as applied).

Group IV: For oral administration, approximately 10-13 mg/kg bw of a 0.067% aqueous dilution of ^{14}C-labelled test substance was administered to each animal.

Group V: approximately 10-12 mg/kg bw of a 0.2% aqueous dilution of ^{14}C-labelled test substance was administered to each animal. In one male, approximately 9.25 mg/kg bw (in 0.5 mL Tyrode solution) was used (see below).

Study Design:
Cutaneous Application
Group I: 200 mg of formulation was applied to an area of 10 cm^2 of intact clipped skin under semi-occlusive conditions without rinsing (test substance dose of 0.045 mg/cm^2). Faeces and urine were analysed daily. Animals were sacrificed after 2 days and treated skin and carcasses were analysed. Two animals were used to analyse the exhalation rate of [^{14}C]-CO_2 during the study.

Group II: 400 mg of formulation was applied to an area of 8 cm^2 of intact clipped skin under semi-occlusive conditions for 30 minutes (test substance dose of 0.058 mg/cm^2). Faeces and urine were analysed at the beginning and end of the study. The animals were sacrificed after 24 hours and the treated skin was analysed.

Group III: 400 mg of form1 or 500 mg of form 2 was applied to an area of 8 cm^2 or 10 cm^2, respectively of intact clipped skin under semi-occlusive conditions for 30 minutes (test substance dose of approx. 0.120 mg/cm^2). Faeces and urine were analysed at the beginning and end of the study. The animals were sacrificed after 24 hours and the treated skin was analysed.

Subcutaneous (s.c.) and Intravenous (i.v.) Administration
Group V: a single s.c. administration; i.v. administration in one male. Faeces and urine were taken as daily fractions over seven days. The carcasses were analysed after the 168 hours observation period. The rate and pattern of excretion was determined 48 hours after i.v. administration; the following organs were analysed: liver, kidney, heart, spleen, lungs, stomach, small intestine, large intestine, caecum, muscle, fat (in muscle and intestine) and blood.

Oral Administration
Group IV: a single oral administration. Faeces and urine were taken as daily fractions over four days. The gastrointestinal tract and carcasses were analysed after the 96 hours observation period.

Findings:

Cutaneous Application
Group I: the mean cutaneous penetration of the test substance was 2.65% and 2.83% for males and females, respectively. Excretion was mainly via urine (83% males/88% females) and to a lesser extent via faeces (7.7% males/4.6% females). The exhaled ^{14}C-concentration in all animals was below the detection limit.

Group II: the mean cutaneous penetration of the test substance was 0.25% (0.15 $\mu g/cm^2$) in males and 0.27% (0.153 $\mu g/cm^2$) in females. The test substance was almost completely excreted via urine. The [^{14}C]-concentration in faeces and carcasses was below detection limits.

Group III: the mean cutaneous penetration of the test substance was 0.48% (0.58 $\mu g/cm^2$) in males and 0.3% (0.29 $\mu g/cm^2$) in females with a coupler, and 0.64% (0.62 $\mu g/cm^2$) in males and 0.35% (0.33 $\mu g/cm^2$) in females without a coupler. The test substance was almost completely excreted via urine.

Subcutaneous and Intravenous Administration
Group V: 98% and 82% of test substance was excreted in urine after s.c. administration, whereas 5% and 19% was excreted in faeces of males and females, respectively. Excretion was completed within 48 hours. No parent substance was detected in the urine of rats. Metabolite identification was not attempted.

Following i.v. administration, 94% was excreted in urine and approx. 2.4% in feces. Less than 0.1% was lost by exhalation. Marginal radioactivity was detected in organs, with the highest level in the stomach and the large intestine (0.18% and 0.11%, respectively).

Oral Administration
Group IV: the mean oral absorption of the test substance via the intestines was 28.2% for females and 41.4% for males; 24.3% and 39.6, for females and males respectively, was excreted via urine within 24 hours. Excretion in faeces was 70.2% for females and 64.3% for males.

At the end of the study, minor amounts of the test material were detected in carcass and gastrointestinal tract.

Comment:
The notified chemical showed low dermal absorption/percutaneous penetration, with almost complete, rapid excretion via the urine of any absorbed dose. Absorption across the intestine was moderate, followed by rapid excretion, predominantly via the faeces. Organ accumulation was very low following either oral or topical administration or i.v. The presence of coupler had very little influence on dermal absorption.

9.2 Acute Toxicity

9.2.1 Oral Toxicity (Potokar 1982a) (Potokar 1982b)

Test Substance:	Notified chemical
Species/strain:	Mice/CF1
Number/sex of animals:	60 males, 10/dose.
Observation period:	7 days
Method of administration:	A single dose of 1 990, 2 510, 3 160, 5 010, 6 310, or 7 940 mg/kg bw (dose volume 40 mL/kg bw) by gavage
Test method:	OECD TG 401
Mortality:	Not indicated
Comment:	Test animals were reported to be apathic for a period. No other observations were reported.
LD_{50}:	4 700 mg/kg bw
Result:	The notified chemical was of very low acute oral toxicity in mice.

9.2.2 Oral Toxicity (Kastner 1982a) (Kastner 1982b)

Two independent experiments were conducted using either 1.6% or 4.2% of notified chemical in hair dye formulations.

Test Substances:	Experiment 1: Formulation 1: Basic hair dyeing cream; Formulation 2: Basic hair dyeing cream supplemented with 1.6% notified chemical as a developer and 1% of coupler (2,7 dihydroxy napthalene). Experiment 2: Formulation 1: Basic hair dyeing cream; Formulation 2: Basic hair dyeing cream supplemented with 4.2% notified chemical as a developer and 2% of a coupler (2-methyl resorcinol).
Species/strain:	Rat/Wistar
Number/sex of animals:	5/sex/Formulation
Observation period:	14 days
Method of administration:	a single dose of 5 000 mg/kg bw as an aqueous dilution (25% w/v) of formulations (dose volume 20 mL/kg bw) by gavage;
Test method:	OECD TG 401- Limit test
Mortality:	None
Comment:	In both experiments, slight piloerection was observed in animals shortly following administration of the test substance formulations. No other clinical symptoms were observed. No treatment related effects were observed at necropsy.
LD_{50}:	5 000 mg/kg bw for all formulations
Result:	Hair dye formulations containing the notified chemical at 1.6% or 4.2% were of very low acute oral toxicity in rats.

9.2.4 Dermal Toxicity

The notifier advises no data are available on this toxicological endpoint.

9.2.5 Inhalation Toxicity

The notifier advises no data are available on this toxicological endpoint.

9.2.6 Skin Irritation in Rabbits (Potokar 1982c)

Test Substance:	notified chemical
Species/strain:	Rabbit/New Zealand white
Number/sex of animals:	6 males
Observation period:	3 days
Method of administration:	A single, 24 hour occlusive, application of 0.5 mL of test substance (10%) to shorn intact dorsal skin.
Test method:	OECD TG 404
Comment:	Draize scores were not submitted with the study. slight redness was reported in two animals shortly after removal of the patch. The test substance was reported as neither irritating nor corrosive under the conditions of the test
Result:	The notified chemical at 10% was slightly irritating to the skin of rabbits.

9.2.7 Skin Irritation in Rabbits (Kastner 1982c, Kastner 1982d)

Two independent experiments were conducted using either 1.6% or 4.2% of notified chemical in hair dye formulations.

Test Substances:	<u>Experiment 1:</u> Formulation 1: Basic hair dyeing cream; Formulation 2: Basic hair dyeing cream supplemented with 1.6% of the notified chemical as a developer and 1% of a coupler (2,7-dihdroxynaphthalene). <u>Experiment 2:</u> Formulation 1: Basic hair dyeing cream; Formulation 2: Basic hair dyeing cream supplemented with 4.2% of the notified chemical as a developer and 2% of a coupler (2-methyl resorcinol).

	Shortly before application, all formulations were mixed with an equal amount of 6% aqueous hydrogen peroxide.
Species/strain:	Rabbit/New Zealand white
Number/sex of animals:	5 males/experiment
Observation period:	Up to 7 days
Method of administration:	For both experiments, a single, 4 hour, occlusive application of 0.5 mL of formulation applied to shorn intact skin, one formulation per flank
Test method:	OECD TG 404
Comment:	No Draize scores were submitted with the study. Experiment 1: slight redness was reported in a few animals up to 48 hours after removal of the patch. Experiment 2: slight redness was reported in two animals treated with Formulation 1 shortly after removal of the patch. The notified chemical in formulation was reported as neither irritating nor corrosive under the conditions of the test
Result:	Hair dye formulation containing the notified chemical at 1.6% was slightly irritating. However, at 4.2% it was non irritating to rabbit skin

9.2.9 Skin Irritation in Humans (Potokar 1983a)

Test Substance:	notified chemical
Volunteers:	5 adults, each test person served as its own control
Observation period:	Immediately following application
Method of administration:	A single, 8 hour occlusive application of test substance (10%) to intact brachial skin of each volunteer
Test method:	Marzulli & Maibach (1975) Food Cosmet Toxicol 13:553-540
Comment:	No treatment related effects were reported. No scores were provided. The test substance was reported as neither irritating nor

corrosive under the conditions of the test.

Result: The notified chemical at 10% was non-irritating to human skin

9.2.10 Skin Irritation - Repeated Application (Potokar 1983b)

Test Substance: Notified chemical

Species/strain: Rabbits/New Zealand white

Number/sex of animals: 2 males

Observation period: 30 minutes

Method of administration: One to two drops of a 10% dilution of the test substance were applied and gently massaged into a small area of shorn intact skin of each animal. The application was repeated every 30 seconds during a 30 minutes time period to the same area of skin. Animals were examined continuously for signs of erythema and oedema.

Test method: Burckhardt (1970) Berufsdermatosen 18:179-188

Comment: No primary skin irritation was reported.

Repeated application of the test substance was reported to not cause skin irritation.

Result: Repeated application of hair dye formulation containing the notified chemical at 10% was non-irritating to rabbit skin

9.2.11 Skin Irritation in Humans - Repeated Application (Potokar 1983c)

Test Substance: notified chemical

Volunteers: 5 adults, each test person served as its own control

Observation period: 30 minutes

Method of administration: One to two drops of a 10% dilution of the test substance were applied and gently massaged into a small area of the skin of the forearm. The application was repeated every 30 seconds for a period of 30 minutes to the same area of skin. Test individuals were examined continuously for signs of erythema and oedema.

Test method: Burckhardt (1970) Berufsdermatosen 18:179-188

Comment: No primary skin irritation was reported.

	Repeated application to the test substance was reported not to cause skin irritation.
Result:	Repeated application of the notified chemical at 10% was non-irritating to human skin

9.2.12 Skin Irritation in Hairless Mice - Repeated Application- (Potokar 1982d)

Test Substance:	notified chemical
Species/strain:	Mice/hr/hr- hairless
Number/sex of animals:	5 males, each animal served as its own control
Observation period:	5 days
Method of administration:	One to two drops of a 10% dilution of the test substance were applied to and gently massaged into a small area of the skin on the back of each animal. The application was repeated twice daily for five consecutive days to the same area of skin. Animals were examined continuously for signs of erythema and oedema.
Test method:	Not described.
Comment:	During and after application no primary skin irritation was reported. Repeated application to the test substance was reported not to cause skin irritation.
Result:	Repeated application of the notified chemical at 10% was non-irritating to the skin of hairless mice

9.2.13 Skin Irritation in Hairless Mice - Repeated Application (Kastner 1983a)

Test Substances:	Formulation 1: Basic hair dyeing cream; Formulation 2: Basic hair dyeing cream supplemented with 1.6% of the notified chemical as a developer and 1% of a coupler (2,7-dihydroxynaphthalene). Shortly before application, both formulations were mixed with an equal amount of 6% aqueous hydrogen peroxide.
Species/strain:	Mice/hr/hr- hairless
Number/sex of animals:	8 males/formulation, each animal served as its own control
Observation period:	5 days
Method of administration:	One to two drops of the formulations were applied to a small area of the skin on the back of each animal; the test substances were washed off 30 minutes following application and skin reactions assessed. The application was repeated once daily for five consecutive days to the same area of skin.
Test method:	Not described.
Comment:	Some animals were reported to show slight erythema following the 2nd and 3rd treatments, which increased after the 4th and 5th applications. Skin reactions were almost non-detectable three days after the last treatment. No symptoms of systemic toxicity were reported.
Result:	Repeated application of hair dye formulation containing the notified chemical at 1.6% was slightly to mildly irritating to the skin of hairless mice

9.2.14 Eye Irritation in Rabbits - (Potokar 1982e)

Test Substance:	notified chemical
Species/strain:	Rabbit/New Zealand white
Number/sex of animals:	6 males
Observation period:	3 days
Method of administration:	0.1 mL of 5% aqueous dilution of the test substance was instilled into the conjunctival sac of one eye of the test animal; test substance remained in permanent contact with the eye. The opposite eye served as a control.

Test method:	OECD TG 405
Comment:	Draize scores were not reported. Slight irritation of the conjunctivae, persisting for 6 hours was reported. However, the number of animals affected was not reported. Neither the cornea nor the iris, were reported as being affected by the test substance.
Result:	The notified chemical at 5% was slightly irritating to rabbit eye

9.2.15 Eye Irritation in Rabbits (Kastner 1982e)

Test Substances:	Formulation 1: Basic hair dyeing cream; Formulation 2: Basic hair dyeing cream supplemented with 1.6% of the notified chemical as a developer and 1% of a coupler (2,7-dihydroxynaphthalene). Shortly before instillation, both formulations were mixed with an equal amount of 6% aqueous hydrogen peroxide.
Species/strain:	Rabbit/New Zealand-white
Number/sex of animals:	5 males/Formulation
Observation period:	3.5 days
Method of administration:	A single, 10 second, instillation of 0.1 mL of test substance into the conjunctival sac of one eye of the test animal, followed by rinsing with 60 mL of tap water. The opposite eye served as a control. The cornea was further investigated for potential injuries with fluorescein.
Test method:	OECD TG 405
Comment:	The cornea in some animals was reported as slightly affected (nature of lesion was not defined) at the 24-hour observation point, irrespective of the test substance formulation. Slight irritation of the conjunctivae was also reported. No other details were provided.
Result:	Hair dye formulation containing the notified chemical at 1.6% was slightly irritating to rabbit eye

9.2.16 Skin Sensitisation - Modification of Magnusson-Kligman Test (Potokar 1982e)

Test Substance:	Notified chemical

Species/strain:	Guineapig/Pirbright white
Number of animals:	Test group: 20 males; Control group: 10 males
Induction procedure:	Full details of the study were not supplied.
day 1	Test Animals: 0.1 mL of an aqueous solution consisting of 5 parts test substance, 7.5 parts dimethylsulfoxide (pH adjusted to 9-9.5 with ammonium hydroxide) and diluted in a 1:1 mixture with Freund's Complete Adjuvant (FCA) was intradermally injected. The treatment was repeated every 2 to 3 days over ten days. Control animals: No details were supplied.
Challenge procedure:	
day 14	Animals were challenged with 0.1 mL of 5% test substance in ethanol applied to the flanks under occlusive dressing for 24 hours;
day 16	Animals were re-challenged in the same way and re-examined after a further 24 and 48 hours.
Test method:	OECD TG 406- Modification of Magnusson and Kligman
Comment:	Skin irritation and reactions consistent with FCA irritation were reportedly observed in all animals during the induction period. Following two challenge applications, no skin changes were reported
Result:	The notified chemical was non sensitising to guineapig skin at a challenge concentration of 5%.

9.2.17 Skin Sensitisation - Magnusson-Kligman Test (Kastner 1983b) (Kastner 1982f)

Two independent experiments were conducted using either 1.6% or 4.2% of notified chemical in hair dye formulations.

Test Substances:

Experiment 1:
Formulation 1: Basic hair dyeing cream;
Formulation 2: Basic hair dyeing cream supplemented with 1.6% of the notified chemical as a developer and 1% of a coupler (2,7-dihydroxynaphthalene).

Experiment 2:
Formulation 1: Basic hair dyeing cream;
Formulation 2: Basic hair dyeing cream supplemented with 4.2% of the notified chemical as a developer and 2% of a coupler (2-methylresorcinol).

Shortly before administration all formulations were mixed with an equal amount of 6% aqueous hydrogen peroxide.

Species/strain:

Guineapig/Pirbright white

Number of animals:

Test groups: 20 females/formulation;
Control group: 10 females/experiment

Induction procedure:

day 1

Test animals:
The following intradermal injections:

- FCA;
- 1% (w/v) aqueous suspension of the test formulation;
- 2% (w/v) aqueous suspension of the test formulation in 1:1 (v/v) FCA;

day 7

Topical induction: dermal application of the test formulation (5% w/w in vaseline) under occlusive dressing for 48 hours.

Control animals were treated similarly but omitting the test substance.

Challenge procedure:

day 21

Animals were challenged with 0.1 mL of 1% w/v (in water) aqueous solution of test formulation applied to the flanks (open conditions);

day 28

Animals were re-challenged with 0.03 mL of 1% w/v (in water) aqueous solution of test formulation applied to the opposite flanks for 24 hours under occlusive conditions using a

	Finn Chamber.
Test method:	OECD TG 406- Magnusson and Kligman
Comment:	In both experiments, skin irritation was evoked by the test formulation in both induction periods and typical reactions to FCA were reportedly observed in all animals. No delayed hypersensitivity was detected in test and control groups. Formulation-related systemic toxicity was not detected in any of the animals.
Result:	Hair dye formulations containing the notified chemical at a challenge concentration of less than 0.01% were non sensitising to guineapig skin

9.3 Repeated Dose Toxicity- 90 Day Feeding Study (Potokar 1978)

Species/strain:	Rats/Wistar
Number/sex of animals:	10/sex/dose group
Method of administration:	*Ad libitum*
Dose/Study duration:	0, 50, 500, and 5 000 ppm (0, 3, 30, and 300 mg/kg bw/day) mixed in animal feed for 13 weeks. The highest dose (5 000 ppm) was increased to 10 000 ppm (600 mg/kg bw/day) after five weeks of dosing.
Test method:	OECD TG 408

Clinical observations:
The test substance was tolerated by the animals after feeding a diet containing up to 10 000 ppm (corresponding to 568-663 mg/kg bw) over 13 weeks.

Body weight gain and water consumption in treatment groups were generally comparable to the control group. Yellowish coloured urine was observed in the highest dose group beginning after one week of administration. The author of the study concluded that the test substance was absorbed intestinally by the animals and excreted in urine.

Clinical chemistry/Haematology
No data were supplied.

Pathology:
Organ weights were unremarkable. No lesions were reported in any of the test group following histopathological examination of the tissues.

The study author reported that no cumulative systemic toxicity was observed at any of the

doses.

Comment:
A complete set of results was not available to enable comprehensive assessment.

Result:
The No Observed Adverse Effect Level (NOAEL) was stated as 600 mg/kg bw/day, the highest dose tested.

9.4 Developmental Toxicity (Potokar, Sudkamp & Pittermann 1980)

Test substance:	Notified chemical
Species/strain:	Rat/Wistar MuRa 67 Han SPF
Number/sex of animals:	20-26/female (for test and control groups)
Method of administration:	Oral (gavage)
Dose/Study duration:	0, 250, 500 or 1 000 mg/kg bw administered daily from days 6 to 19 of gestation; Dams were sacrificed on day 20 of gestation.
Test method:	Not reported, but similar to OECD TG 414

Maternal in-life findings:
No indication of maternal toxicity was observed in dams at up to 500 mg/kg bw/day. Slight retardation of the mean body weight gain was observed at 1 000 mg/kg bw/day.

Foetal findings:
Administration of up to 500 mg/kg bw/day of the test substance had no adverse effects on foetal development.
At 1 000 mg/kg bw/day, the mean implantation loss was slightly increased. However, treatment-related foetal lesions or malformations were not evident.

Comment:
Based on these observations, the test substance was considered by the study author to be neither lethal nor toxic to the embryo and not teratogenic.

Result:
The No Observed Adverse Effect Level (NOAEL) for foetal effects was reported to be 500 mg/kg bw/day. An NOAEL for maternal toxicity was not reported in the summary data provided.

9.5 Genotoxicity

9.5.1 *Salmonella typhimurium* Reverse Mutation Assay (Wallat 1980)

Test substance:	Notified chemical

Strains:	TA 98, TA 100, TA 1535, TA 1537 and TA 1538
Concentration range:	Test substance: 2.7 μg/plate to 6 750 μg/plate; no further details were supplied. Positive control: p-Toluenesulfonic acid hydrazid with TA 100 and TA 1535; o-nitro-p-phenylenediamine with TA 98, TA 1537 and TA 1538 Negative control: DMSO and water
Metabolic activation:	Liver fraction (S9) from rats pretreated with Aroclor 1254 or phenobarbital
Test method:	OECD TG 471
Comment:	The test substance was investigated at the given pH and at pH 8.5 or 9.5 (adjusted using ammonium hydroxide). The test substance failed to induce reverse mutations in the strains tested both in the absence and presence of metabolic activation, irrespective of pH.
Result:	The notified chemical was non-mutagenic in the bacterial strains tested in the presence or absence of metabolic activation under the conditions of the experiment

9.5.2 **Chromosomal Aberration Assay in Chinese Hamster Lung V79 Cells *in vitro***

(Heidemann 1990)

Test substance:	Notified chemical
Cell line:	Chinese hamster lung cells, V79
Metabolic activation system:	Liver fraction (S9) from rats pretreated with Aroclor 1254
Doses:	Duplicate cultures were used to test each concentration, with or without metabolic activation; Concentration range: 0.6 to 17 μg/mL; Treatment interval: 4 hours; Harvest time: 7 hours (high dose), 18 hours (low, medium and high dose), 28 hours (high dose). Appropriate reference materials were used as positive controls.
Test method:	OECD TG 473
Comment:	Full study details were not supplied. The plating efficiency of V79 cells was not reduced with up to 17 μg/mL. However, the mitotic index was reduced with the highest dose only at 7 hours fixation interval in the absence of metabolic activation. It was reported that concentrations higher than 17 μg/mL were insoluble. No increase in cells with structural chromosome aberrations following treatment with the test substance at any fixation interval with or without metabolic activation.
Result:	The notified chemical was non-clastogenic *in vitro* under the conditions of the experiment.

9.5.3 Micronucleus Assay in the Bone Marrow Cells of the Mice (Richold M and Richardson J 1980)

Test substance:	Notified chemical
Species/strain:	Mice/CD1
Number and sex of animals:	Range finding study: 2/sex/dose (total: 24 animals); Main study: 5/sex/dose.
Doses:	0, 100, 5 000 and 10 000 mg/kg bw suspended in 1% carboxymethylcellulose. Positive control: 4 mg/kg mitomycin C; Negative control: 1% carboxymethylcellulose.
Method of administration:	Each dose was administered in two equal portions by gavage, 24 hours apart.
Test method:	OECD TG 474
Comment:	The author reported that the test substance did not show any evidence of mutagenic potential *in vivo*.
Result:	The notified chemical was non-clastogenic *in vivo* under the conditions of the experiment

9.6 Overall Assessment of Toxicological Data

The submission contained summary data on study reports on the notified chemical, TAP, which had been submitted to the European Cosmetic, Toiletry and Perfumery Association (COLIPA). Studies were conducted on neat notified chemical, aqueous dilutions of the notified chemical, or the notified chemical in combination with other components of hair dye formulations to mimic the end use application.

The ability of the notified chemical to penetrate the skin was investigated *in vivo* on rat skin. Application of a basic cream containing the notified chemical (but without a coupler or developer), showed low percutaneous absorption of TAP (2.65 to 2.83%) with excretion mainly via urine (83 to 88% over 48 hours). Similarly, percutaneous absorption measured over 24 hours following exposure for 30 minutes of a dye formulation with and without different couplers and developer, was very low (maximum of 0.64%) with excretion almost completely via urine. Following oral dosing, absorption across the intestine was 28.2 to 41.4%. Between 24.3 to 39.6% was excreted via urine, 64.3 to 70.2% was excreted via faeces, and minor concentrations were detected in the GIT and carcass. Excretion was rapid, with the majority of the absorbed dose by both percutaneous and oral routes excreted within 24 hours. Following subcutaneous or intravenous administration, the majority of administered radioactivity was excreted via urine.

The notified chemical was of very low oral toxicity in mice (LD_{50} 4 700 mg/kg). A single, 24 hour application of the notified chemical at 10% under occlusive conditions was reportedly slightly irritating to rabbit skin. Following repeated application of a 10% aqueous solution, under

non occlusive conditions, the notified chemical was reportedly non-irritating to the skin of hairless mice, rabbits or human volunteers. Slight irritation was observed in rabbit eye following instillation of the notified chemical at 5%. The notified chemical was non-sensitising to guineapig skin in an adjuvant type study at a challenge concentration of 5%.

In a 90 day repeat oral dose study in rats, no cumulative toxic effects were reported at any of the doses examined. The NOEL was 600 mg/kg bw/day, the highest dose tested. In a developmental study in rats, no evidence of maternal toxicity, teratogenicity or foetal toxicity were observed at 500 mg/kg bw/day of test substance. The high dose (1 000 mg/kg bw/day) showed a slight increase in the mean implantation loss. The NOAEL for developmental toxicity was 500 mg/kg bw/day. An NOAEL for maternal toxicity was not reported.

The notified chemical was considered non mutagenic in *Salmonella*. It was non clastogenic *in vitro* or *in vivo.*

Investigations into acute oral toxicity, skin irritancy and skin sensitisation using hair dye formulations with or without the notified chemical revealed a toxicological profile similar to investigations on the notified chemical or hair dye formulation alone. These findings suggest that under end use conditions, any effects observed with the notified chemical are not exacerbated in the presence of other components of the hair dye.

Hazard Classification
The notified chemical was of very low oral acute toxicity and at a challenge concentration of 5% was non sensitising to skin. Following repeat dose testing it did not cause systemic or organ toxicity or developmental effects. Genotoxic potential was not revealed in *in vitro* or *in vivo* studies. The notified chemical would not be classified as a hazardous substance under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1999) in terms of the toxicological end points investigated.

Given that the degree of irritation was reported as slight, aqueous dilutions of the notified chemical at 5% or 10% are unlikely to require classification as eye or skin irritants, respectively, under the *Approved Criteria for Classifying Hazardous Substances* given. Assessment of eye and skin irritancy for the notified chemical at 100% cannot be made in the absence of testing at this concentration.

10. ASSESSMENT OF ENVIRONMENTAL EFFECTS

No ecotoxicological data were provided which is acceptable for chemicals with import volumes < 1 tonne per year according to the Act.

The following table is a summary of the ecotoxicological data estimated by the ASTER model for the pyrimidine free base.

ASTER Generated Ecotoxicological Data

Acute Effect	48 hour LC_{50}	Water Flea (*Daphnia magna*)	9.6 g/L
		Fathead minnow	25.3 g/L
	96 hour LC_{50}	Bluegill	17.3 g/L
		Rainbow Trout	14.1 g/L
Chronic Effect	32 days	Fathead minnow	2.6 g/L

This data suggests that the chemical is practically non-toxic to aquatic organisms.

11. ASSESSMENT OF ENVIRONMENTAL HAZARD

The estimated amount of notified chemical reaching the environment though spills and container residues is around 3%, ie 12 kg per annum. This 12 kg will most probably end up in a landfill or may be incinerated. The unreacted chemical is likely to leach out of a landfill, however, this will be in low concentrations and in a diffuse manner.

Most of the chemical will react with the other dye components before being adsorbed to hair, so when rinsed from the hair less than 50% of the dye will end up in the sewer. If the dye has been mixed correctly the rinsate will not contain any unreacted chemical.

An unlikely worst case scenario would be if a number of bottles lost their contents into the sewer. If we assume that the contents of 100 bottles (5L of product, corresponding to 140g of notified chemical). The Predicted Environmental Concentration (PEC) is as follows:

Metropolitan STP:	Unreacted notified chemical released	140 g
	Water handled by the STP	250 ML/day
	Dilution in receiving water	1:10
	PEC in receiving water	0.056 ppb

This PEC is orders of magnitude less than the ASTER estimated toxicity to daphnia or trout. It may be concluded that the hazard posed by the chemical is very low.

12. ASSESSMENT OF PUBLIC AND OCCUPATIONAL HEALTH AND SAFETY EFFECTS

The notifier provided summary reports on the notified chemical TAP, which had been submitted to COLIPA.

Toxicokinetic studies with a hair-dye formulation of TAP revealed a low percutaneous absorption (maximum of 0.64%) after a 30 minute exposure with almost complete excretion of radiolabel in the urine within 24 hours. Absorption was not affected by normal hair dye components.

The notified chemical was of very low oral acute toxicity and at 10% was slightly irritating to rabbit skin, but non-irritating to human skin. Repeat application of the notified chemical was reported as non irritating to mouse, rabbit and human skin. The notified chemical tested at 5% was slightly irritating to rabbit eyes. The notified chemical, at a challenge concentration of 5% was non sensitising to guineapig skin.

In a 90 day repeat dose dietary study, no cumulative toxic effects were reported at any of the doses examined. The NOAEL was 600 mg/kg bw/day. In a reproductive toxicity study, the NOAEL for developmental toxicity was 500 mg/kg bw/day. An NOAEL was not reported for maternal toxicity.

Investigations of mutagenicity in bacteria or clastogenicity *in vitro* or *in vivo* revealed no genotoxic potential.

No adverse effects have been reported for a near identical chemical during its use in Australia under a Low Volume Chemical permit.

Based on the findings of investigations into acute and repeat oral dosing, sensitisation and genotoxicity, the notified chemical is not classified as a hazardous substance under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1999).

Occupational Health and Safety
The notified chemical will be imported as an ingredient (2.8% w/w) of a hair colour product in retail bottles (50 mL). No reformulation or repackaging will be undertaken. The imported hair dye product will be distributed to supermarkets and retailers Australia-wide; it will be available for direct use by the public.

Exposure to the notified chemical during transport or storage would only occur in the event of a spill. Exposure after a spill would be controlled by use of the recommended practices for spillage clean up given in the Material Safety Data Sheet (MSDS) supplied by the notifier. Given the non-toxic nature of the notified chemical and its low concentration in the product, the risk of adverse health effects for transport, storage and retail workers is considered negligible.

Public Health Effects
Based on the brief summaries provided for the range of toxicological studies performed on TAP, this compound presents little toxicological hazard at the levels of use, and for the purpose, proposed by the notifier. As exposure, whilst potentially widespread, will be intermittent, limited to the dermal route, and of short duration, the potential for adverse effects is negligible. This conclusion is strengthened by the demonstrated low level of dermal penetration of, and

consequent negligible systemic exposure to TAP.

Accordingly, TAP is not considered to pose a significant hazard to public health.

13. RECOMMENDATIONS

To minimise occupational exposure to hair dye formulations containing TAP during transporting and handling the following guidelines and precautions should be observed:

- Industrial clothing should conform to the specifications detailed in AS 2919 (Standards Australia 1987) and AS 3765.1 (Standards Australia 1990); all occupational footwear should conform to AS/NZS 2210 (Standards Australia/Standards New Zealand 1994);
- Spillage of the notified chemical should be avoided. Spillages should be cleaned up promptly with absorbents which should be put into containers for disposal;
- Good personal hygiene should be practised to minimise the potential for ingestion; and
- A copy of the MSDS should be easily accessible to employees.

If the conditions of use are varied, greater exposure of the public to the notified chemical may occur. Under such circumstances, further information may be required in order to assess the risks to public health.

14. MATERIAL SAFETY DATA SHEET

The MSDS for a typical hair dye formulation containing the notified chemical was provided in a format consistent with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 1994).

This MSDS was provided by the applicant as part of the notification statement. It is reproduced here as a matter of public record. The accuracy of this information remains the responsibility of the applicant.

15. REQUIREMENTS FOR SECONDARY NOTIFICATION

Under the Act, secondary notification of the notified chemical shall be required if any of circumstances stipulated under subsection 64(2) of the Act arise. No other specific conditions prescribed.

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