File No.: LTD/2149

September 2020

AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME (AICIS)

PUBLIC REPORT

Phenol, 2-chloro-4-[(1*E*)-2-[3-(methylthio)-1,2,4-thiadiazol-5-yl]diazenyl]- (INCI name: HC Red No. 18)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals Act 2019* (the IC Act) and *Industrial Chemicals (General) Rules 2019* (the IC Rules) by following the *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Act 2019* (the Transitional Act) and *Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019* (the Transitional Rules). The legislations are Acts of the Commonwealth of Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) is administered by the Department of Health, and conducts the risk assessment for human health. The assessment of environmental risk is conducted by the Department of Agriculture, Water and the Environment.

This Public Report is available for viewing and downloading from the AICIS website. For enquiries please contact AICIS at:

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Executive Director
AICIS

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SUMMARY

The following details will be published on our website:

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2149	Kao Australia Pty Ltd	Phenol, 2-chloro-4-[(1*E*)-2-[3-(methylthio)-1,2,4-thiadiazol-5-yl]diazenyl]- (INCI Name: HC Red No. 18)	Yes	≤ 0.07 tonne per annum	Oxidative hair dye ingredient for professional use only

CONCLUSIONS AND REGULATORY OBLIGATIONS

Health Hazard Classification
Based on the studies evaluated by the SCCS (2016), the assessed chemical is a hazardous chemical according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia. The hazard classification applicable to the assessed chemical is presented in the following table.

Hazard Classification	*Hazard Statement*
Specific Target Organ Toxicity – Repeated exposure (Category 2)	H373 – May cause damage to organs through prolonged or repeated exposure

Human Health Risk Assessment
Under the conditions of the occupational settings described, the assessed chemical is not considered to pose an unreasonable risk to the health of workers.

When used in the proposed manner, the assessed chemical is not considered to pose an unreasonable risk to public health

Environmental Risk Assessment
On the basis of the reported use pattern and import volume of less than one tonne, the assessed 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 safe work practices to minimise occupational exposure during handling of the assessed chemical as introduced in hair dye products:
  - Avoid contact with skin and eyes

- 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 assessed chemical as introduced in hair dye products:
  - Impervious gloves

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

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

- If products and mixtures containing the assessed 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.

Emergency procedures

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

Disposal

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

Regulatory Obligations

Specific Requirements to Provide Information
This risk assessment is based on the information available at the time of the application. The Executive Director may initiate an evaluation of the chemical based on changes in certain circumstances. Under section 101 of the IC Act the introducer of the assessed chemical has post-assessment regulatory obligations to provide information to AICIS when any of these circumstances change. These obligations apply even when the assessed chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

Therefore, the Executive Director of AICIS must be notified in writing within 20 working days by the applicant or other introducers if:

- the function or use of the assessed chemical has changed from hair dye for professional use only, or is likely to change significantly;
- the importation volume exceeds one tonne per annum assessed chemical;
- the assessed chemical has begun to be manufactured in Australia;
- the assessed chemical is imported for reformulation in Australia;
- the concentration of the assessed chemical in hair dye products has increased from 1.5%;
- the on head concentration of assessed chemical has increased from 0.5%; and
- additional information has become available to the person as to an adverse effect of the chemical on human health, or the environment.

The Executive Director will then decide whether an evaluation of the introduction is required.

Safety Data Sheet.
The SDS of the products containing the assessed chemical provided by the applicant were reviewed by AICIS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND APPLICATION DETAILS

APPLICANT(S)
Kao Australia Pty Ltd (ABN: 059 054 708 299)
Level 2, 293 Camberwell Road
CAMBERWELL VIC 3124

APPLICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year)

PROTECTED INFORMATION (SECTION 38 OF THE TRANSITIONAL ACT)
Data items and details taken to be protected information include: analytical data, degree of purity, use details and import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 6 OF THE TRANSITIONAL RULES)
Schedule data requirements are varied for all physical and chemical properties.

PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT(S)
None

APPLICATION IN OTHER COUNTRIES
EU: REACH

2. IDENTITY OF CHEMICAL

MARKETING NAME
HC Red 18 (INCI Name)

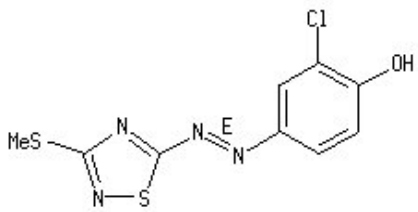
CAS NUMBER
1444596-49-9

CHEMICAL NAME
Phenol, 2-chloro-4-[(1*E*)-2-[3-(methylthio)-1,2,4-thiadiazol-5-yl]diazenyl]-

OTHER NAME(S)
FPK-245
Colipa No. B124

MOLECULAR FORMULA
$C_9H_7ClN_4OS_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
286.76 g/mol

ANALYTICAL DATA
Reference NMR, FT-IR and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 99.3%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: orange/red powder

Property	*Value*	*Data Source/Justification*
Melting Point	349.84 °C	Calculated (US EPA MPBVP (v1.43))
Boiling Point	415.64 °C at 101.3 kPa	Calculated (US EPA MPBVP (v1.43))
Density	~1,100-1,200 kg/m^3	Estimated by applicant
Vapour Pressure	2.62 x 10^{-9} kPa at 25 °C	Calculated (US EPA MPBVP (v1.43))
Water Solubility	17.44 mg/L at 25 °C	Calculated using-US EPA (2012) WSKOW (v1.42)
Hydrolysis as a Function of pH	Not determined	Does not contain functionality susceptible to hydrolysis. Found to be stable in alkaline peroxide for 45 min (EU 2015).
Partition Coefficient (n-octanol/water)	log Pow = 3.6 at 25 °C	Calculated using-US EPA (2012) KOWWIN (v1.68)
Adsorption/Desorption	log Koc = 3.91 at 25 °C	Calculated using US EPA (2012) KOCWIN (v2.0)
Dissociation Constant	pKa = 6.57	Calculated using ACD/labs
Flash Point	Not determined	Not expected to form flammable vapours (information provided by the applicant)
Flammability	Not determined	Not expected to be flammable
Autoignition Temperature	Not determined	Not expected to autoignite
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply explosive properties

DISCUSSION OF PROPERTIES

Reactivity
The assessed chemical is expected to be stable under normal conditions of use.

Physical Hazard Classification
Based on the limited physico-chemical data depicted in the above table, the assessed 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 ASSESSED CHEMICAL (100%) OVER NEXT 5 YEARS
The assessed chemical will not be manufactured in Australia. It will be imported into Australia as a component of oxidative hair dye products at ≤ 1.5% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.02-0.07	0.02-0.07	0.02-0.07	0.02-0.07	0.02-0.07

PORT OF ENTRY
Major ports in Australia

IDENTITY OF MANUFACTURER/RECIPIENTS
Kao Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The assessed chemical will be imported as a component of finished hair dying products (at ≤ 1.5% concentration) in containers, such as tubes (50 -120 g) or in tubs (500 g), for professional use only.

USE
The assessed chemical will be used as an oxidative dye in hair dye formulations and will be introduced in end-use products at ≤ 1.5% concentration. The hair dye product will be mixed with a developer to give a maximum on-head concentration of 0.5% for the assessed chemical. The hair dye products will be available for use by professionals only (e.g. hair dressers or hair salon workers).

OPERATION DESCRIPTION
The assessed chemical will not be reformulated or repacked in Australia. Hair dye products containing the assessed chemical at ≤ 1.5% concentration will be used by professionals only (such as hairdressers and beauty salon workers). Professional hairdressers and beauty salon workers will mix the hair dye products with a developer and then apply the dye mixture containing the assessed chemical at ≤ 0.5% concentration to the customer's hair with an applicator brush. The dye is allowed to remain in contact with the hair for 25 minutes, and is then washed out with water, shampoo and conditioner.

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 warehouse	2	12
Professional salon workers	4	220

EXPOSURE DETAILS
Transport, storage and warehouse workers may come into contact with products containing the assessed chemical at ≤ 1.5% concentration, only in the unlikely event of an accidental rupture of containers.

End-use
Dermal exposure to the assessed chemical at ≤ 1.5% concentration in hair dye products may occur to professionals (e.g. hair dressers or beauty salon workers) when mixing and applying the hair dye products to clients. Such professionals may use limited personal protective equipment (PPE), such as impervious gloves, to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers to the assessed chemical is expected to be limited.

6.1.2. Public Exposure
Hair dye products containing the assessed chemical will not be made available for home use. The public will be exposed to hair dye products containing the assessed chemical at 0.5% during hair dye treatments in hair salons. The main route of exposure will be dermal, with some potential for accidental ocular exposure. The maximum on-head concentration of the assessed chemical will be 0.5%.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on the assessed chemical are summarised in the table below, taken from a report by the Scientific Community on Consumer Safety (SCCS, 2016). Study dossiers were not provided by the applicant.

Endpoint	***Result and Assessment Conclusion***
Dermal percutaneous absorption: *in vitro* human dermatomed skin	1.35 µg/cm^2 (0.97 ± 0.38 µg/cm^2) or 0.44 ± 0.17 % of applied dose in 3% cream under oxidative conditions
Skin irritation – *in vitro* EpiDerm™ model)	skin irritating potential cannot be ruled out
Eye irritation – *in vitro* Bovine Corneal Opacity and Permeability (BCOP) test	eye irritating potential cannot be ruled out
Eye irritation – *in vitro* EpiOcular™ human cornea tissue model	eye irritating potential cannot be ruled out

Endpoint	*Result and Assessment Conclusion*
Skin sensitisation – mouse local lymph node assay	no evidence of sensitisation up to 10% concentration
Repeat dose oral toxicity – rat, 14 days	NOAEL (males) = 100 mg/kg bw/day NOAEL (females) = 30 mg/kg bw/day
Repeat dose oral toxicity – rat, 90 days	NOAEL = 3 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian cell gene mutation test (*hprt* locus)	non genotoxic
Genotoxicity – i*n vitro* mammalian cell micronucleus test	non genotoxic
Genotoxicity – i*n vivo* bone marrow micronucleus test	non genotoxic
Reproductive and developmental toxicity – rat	NOAEL (maternal & development toxicity) = 50 mg/kg bw/day

The SCCS Opinion (2016) commented that reported purity and impurity data indicated for three batches cannot be accepted as there were discrepancies and uncertainties related to the purity of different batches.

Toxicokinetics, Metabolism and Distribution
A toxicokinetics, metabolism and distribution study was conducted in rats, using a radiolabelled form of the assessed chemical (purity: 99.06%), according to OECD TG 417 (2010) and OECD TG 427 (2004).

Excretion in bile, urine and faeces - normal and bile-cannulated rats
Animals were administered the assessed chemical orally (gavage) and percutaneously at a dosage of 3 mg/kg bw and 25 mg/kg bw, respectively. Following percutaneous administration in normal rats (non-cannulated), the assessed chemical was excreted via urine (2.97 ± 1.77%) and faeces (1.89 ± 1.24 %) after 168 hours (7 days) post treatment; the total recovery of radioactivity was 102.35 ± 1.93% of the dose. Similarly, for oral administration, in normal rats, the assessed chemical was excreted via urine (65.49 ± 3.07%) and faeces (30.60 ± 3.71 %) after 168 hours post treatment; the total recovery of radioactivity was 98.22 ± 1.14% of the administered dose. These results indicated that the dosed radioactivity was always completely excreted by 168 hours post-dose, regardless of the dosing route.

In bile-cannulated rats, the assessed chemical was excreted via bile (47.61 ± 9.88%), urine (28.45 ± 6.18%) and faeces (23.59 ± 2.85%) after 48 hours following oral administration. Animals in bile-cannulation showed a lower faecal excretion of radioactive assessed chemical indicating that the assessed chemical was not absorbed by the digestive tract. A recovery of 102.06% of the radiolabelled assessed chemical in bile-cannulated rats were reported by the study authors.

Conclusions
Based on the results obtained, the assessed chemical was rapidly and completely adsorbed and widely distributed after oral administration in rats. The bioavailability after oral administration can be considered as very high (98.14%). Although absorption through the intact skin (dermal application) was significantly lower when compared to the oral administration, the assessed chemical was widely distributed and rapidly excreted via urine (2.97%) and faeces (1.89%) after 168 hours of administration. Irrespective of the route of administration, the assessed chemical was almost completed metabolised and only minor amounts of the unchanged compound were detected. There was no indication of any persistency in any organ or tissue.

According to the SCCS Opinion (2016) noted that after single oral application of the assessed chemical, up to approximately 65% and31% of the dose was excreted in the urine and faeces, respectively, indicating oral absorption of approximately 65% of the dose from the GI tract. In bile-duct cannulated rats, approximately 48%, 29% and 24% of the dose was excreted in the bile, urine and faeces, respectively, indicating oral absorption of up to approximately 77% of the dose from the GI tract (sum of dose excreted in the bile and the urine). Under the conditions of this toxicokinetic study, oral absorption of 77% is considered for the assessed chemical in the SCCS Opinion (based on the results from the bile-duct cannulated rats) and it was used for the correction of the NOAEL for the margin of safety (MoS) calculation.

Dermal / percutaneous absorption
The dermal penetration of the assessed chemical (purity: 99.85%) from two different formulations (non-oxidative and oxidative) containing the assessed chemical at 3% (oxidative conditions) and 1.5% (non-oxidative conditions)

concentration was investigated in dermatomed pig ear skin from 6 different donors according to OECD TG 428 (2004).

Under the reported conditions, the assessed chemical at 3% (oxidative conditions) showed low penetration into the viable skin layers and into the receptor fluid. The dermal penetration was 0.97 ± 0.38 µg/cm² (0.44 ± 0.17% of applied dose). Under non-oxidative conditions, the assessed chemical at 1.5% penetrated into the viable layers and into the receptor fluid indicating the absorption as 2.65 ± 0.78 µg/cm² (1.43 ± 0.49% of applied dose).

Acute Toxicity
No data were submitted for acute oral, dermal and inhalation toxicity.

Skin Irritation
The assessed chemical (purity: 99.85%) was applied to reconstructed human epidermis tissues wetted with deionised water according to OECD TG 439 (2010).

Treatment with assessed chemical did not induce a decrease in the mean relative absorbance value (113.1%) when compared to the relative absorbance of the negative control for the 60 minute treatment interval. Therefore, the assessed chemical was considered to possess no irritant potential to the skin *in vitro* under the experimental conditions of the study.

However, SCCS (2016) noted that the assessed chemical caused the red colouring of the tissues which may have interfered with the test leading to false estimates of the skin irritation potential. Therefore, under the conditions of this study, a skin irritation potential of the assessed chemical cannot be ruled out.

Eye Irritation
Two *in vitro* eye irritation studies were conducted to evaluate the irritation potential of the assessed chemical (purity: 99.85%). When tested at 20% concentration in a Bovine Corneal Opacity and Permeability (BCOP) test according to OECD TG 437 (2009), the assessed chemical caused an increase in the corneal opacity while no permeability effects could be observed. The calculated mean *in vitro* irritancy score (IVIS) of the assessed chemical was 22.07 when compared to negative control (IVIS= 2.71). The study authors concluded that although under the conditions of the test, some irritancy was demonstrated, but it was significantly below the level (threshold for corrosivity / severe irritancy: ≥ 55.1) to consider the assessed chemical as corrosive or a severe eye irritant.

Another *in vitro* eye irritation test was performed on the assessed chemical using the EpiOcular™ human cornea tissue model (test kit manual, 2013; non-guideline study). The tissues were treated with assessed chemical for 3, 30 and 60 minutes. No irritating effects were noted following the treatment with assessed chemical at up to 60 minutes of incubation. Exposure time required to reduce cell viability by 50% (ET_{50} value) could not be calculated due to the lack of cytotoxicity of the assessed chemical. Therefore, the study authors concluded that, under the experimental conditions reported, the assessed chemical does not possess any eye-irritating potential.

However, SCCS (2016) noted that in both *in vitro* tests, the assessed chemical caused the red colouring of the tissues which may have interfered with the tests leading to false estimates of the eye irritation potential. Therefore, under the conditions of these studies, an eye irritation potential of the assessed chemical cannot be ruled out.

Skin sensitisation
The study of the possible allergic potential of the assessed chemical (purity: 99.69%) was done by the local lymph node assay (LLNA) according to OECD TG 429 (2004).

The assessed chemical at 2.5%, 5% and 10% in DMSO produced stimulation indices (SI) of 0.9, 0.9 and 1.5, respectively. The EC3 value could not be calculated, since all SIs are below 3. The assessed chemical was found not to be a skin sensitiser under the described test conditions, up to 10% concentration.

Repeated Dose Toxicity
Repeated Dose (14 days) oral toxicity- range-finding study
In a 14-day dose-range finding study, the assessed chemical (purity: 99.69%) in 0.5% methycellulose solution was administered 50 Crl:CD(SD) rats (25 males and 25 females) at 0, 30, 100, 200 (300), and 600 (1000) mg/kg bw/day. The animals (5 males, 5 females, each concentration) were treated by oral gavage, once daily, for 14 days according to OECD TG 407 (2008). Initial dosing at 300 and 1000 mg/ kg bw/day led to significant decrease in body weight including mortalities, thus were reduced to 200 and 600 mg/ kg bw/day from study day 7 and 10 onwards, respectively.

Seven animals, 2 males and 5 females, treated at 600 mg/kg bw/day died on day 8 and days 6-13, respectively. Three males (treated at 600 mg/kg bw/day) and 2 females (treated at 200 mg/kg bw/day) were humanely killed due to poor clinical condition including decrease in locomotor activity, abnormal gait and decrease in body weight on day 10 and day 6-8, respectively. There were no mortalities or clinical signs for animals treated at lower doses.

A no-observed-adverse-effect-level (NOAEL) for systemic toxicity was considered to be 100 mg/kg bw/day for males and 30 mg/kg bw/day for females based on the significant increase in relative liver weight observed in males and females at 200 and 100 mg/kg bw/day, respectively.

On the basis of the results obtained in the 14-day dose range finding study the following dose levels for the 90 day sub-chronic study were proposed: 0, 3, 30 and 150 mg/kg bw/day.

Sub-chronic (90 days) toxicity (oral)

The animals (n=10/sex/dose) were treated by oral gavage doses of the assessed chemical (purity: 99.85%), once daily for 91 days at 0, 3, 30 and 150 mg/kg bw/day (OECD TG 408, 1997). Control animals were treated with vehicle (0.5% methylcellulose solution) only. Five animals per sex of the control group and high dose group were allowed a 4-week treatment-free recovery period.

At 150 mg/kg bw/day, one female was found dead on day 15; thus the dose was reduced to 75 mg/kg bw/day from day 16 onwards. Another six females either died or were sacrificed in moribundity between days 16-24; thus the dose was further decreased to 50 mg/kg bw/day (day 21 onwards). Similarly, in males, initial dosing at 150 mg/kg bw/day caused severe clinical signs including decreased body weights and food consumption and thus the dose was reduced to 75 mg/kg bw/day (day 37 onwards) and further reducing to 50 mg/kg bw/day (day 44 onwards).

Decreased mean bodyweight was statistically significant in high dose males and females from day 29 and day 15, respectively, but returned to normal (in males) or exceeded to that of the control group in the last week of the recovery period.

Abnormal gait was noted in all surviving animals (5/10 males and 5/10 females) at high dose group (150/75/50 mg/kg bw/day). In addition, a decrease in locomotor activity was observed in 3 of those surviving males and females from day 43 to 58 and day 54 to 61, respectively. These abnormal signs disappeared after the recovery period.

Within the neurofunctional tests, no abnormalities were noted for the sensory reactivity to stimuli or motor activity measurements. The grip strengths were statistically significantly decreased in forelimbs in males and females at the high dose group and in hindlimbs in males and females at 30 mg/kg bw/day and higher in the last week of the dosing period. These changes recovered at the end of the recovery period.

Ophthalmology and urinalysis were not affected in any groups.

The primary treatment-related histopathological changes were observed in the liver and femoral muscle following the scheduled sacrifice after the dosing period. The minimal centrilobular hypertrophy of hepatocytes was observed in males and females at the high dose group.

Atrophy, degeneration and/or regeneration of muscle fibre were observed in males and females with a dose-dependent increased severity at 30 mg/kg bw/day and higher, and was more severe in females that in males. Atrophy of muscle fibre was still observed in males and females after 4-week recovery period, but its grade was minimal. Minimal to mild hypertrophy of muscle fibre was observed in males and females at 150/75/50 mg/kg bw/day, whereas degeneration and regeneration of muscle fibre were not observed in any animals.

In the females that died or were sacrificed in moribundity, atrophy, degeneration and/or regeneration of muscle fibre were observed as in the scheduled sacrifice animals. Their grades were minimal to mild. In dead or moribund sacrifice animals, treatment-related changes were noted in the stomach, thymus, spleen, and femoral muscle at 150/75/50 mg/kg bw/day in the form of blackish patches in the stomach, small thymus, small spleen and in the thinning of femoral muscle in single females.

A NOAEL for systemic toxicity was considered to be 3 mg/kg bw/day for both sexes, based on the atrophy of femoral muscle at 30 mg/kg bw/day.

The SCCS Opinion (2016) agreed with the NOAEL of 3 mg/kg bw/day and this NOAEL was used for the MoS calculation.

Mutagenicity/Genotoxicity
The assessed chemical was negative for the induction of gene mutations in *Salmonella. typhimurium* and *Escherichia coli* (Ames test) according to OECD TG 471 (1997). The assessed chemical was also tested negative for mutations at the *hpr*t locus of Chinese hamster V-79 cell lines both in the absence and presence of metabolic activation according to OECD TG 476 (1997).

The assessed chemical has been tested negative in the absence and presence of metabolic activation for the induction of micronuclei in human lymphocytes according to OECD TG 487 (2010). The assessed chemical was also assessed for the induction of micronuclei in bone marrow cells (as per non-guideline method). In this case, the assessed chemical was administered to rats by oral gavage at dose levels of 0, 30, 100, 200 (300), and 600 (1000) mg/kg bw/day. Under the experimental conditions used, the assessed chemical did not induce any change in the incidence or in the percentage of immature erythrocytes in rats and consequently, was non genotoxic (clastogenic and/or aneugenic).

The SCCS (2016) considered that sufficient investigation of the potential for genotoxicity had been carried out and that the assessed chemical could be considered to have no genotoxic potential. The SCCS (2016) also noted that DMSO (Ames test and micronucleus assay) and deionised water (mammalian gene mutation test) were used as solvents to perform the genotoxicity/mutagenicity tests and the precipitation of the assessed chemical occurred at low concentrations.

Teratogenicity
Dose range-finding study
The assessed chemical (purity: 99.85%) was administered to mated female rats by oral gavage from gestation days 6 to 20 at the doses 0, 50, 100 and 200 mg/kg bw/day (OECD TG 414, 2001). All females were sacrificed on day 21 post-coitum and the foetuses were removed by caesarean section.

At 100 and 200 mg/kg bw/day, animals were sacrificed moribund because of severe clinical symptoms (uncoordinated movement, prostrate, ruffled fur, chromodachryorrhea, reddish nasal secretion and weight loss) noted from day 12. Premature termination of dams was also noted.

At 50 mg/kg bw/day no clinical findings were reported except reddish discoloured urine. All females survived until the scheduled necropsy. Post-implantation losses and the mean number of foetuses per dam were not affected at 50 mg/kg bw/day and no macroscopical findings were noted during necropsy. No treatment-related effects on foetal sex ratios, foetal body weights, and external abnormalities and variations were noted.

Based on these results, the maternal and foetal NOAEL was considered to be 50 mg/kg bw/day and the following dose levels were considered appropriate for the main study: 0, 3, 15 and 50 mg/kg bw/day.

Main study
Eighty-eight animals (22 mated female rats/dose) were treated by oral gavage at doses of 0, 3, 15, 50 mg/kg bw/day with the assessed chemical (purity: 99.85%) from gestation day 6 to 20 (OECD TG 414). Females were sacrificed on day 21 post-coitum and the foetuses were removed after caesarean section. Control animals were dosed with the vehicle alone.

All females survived until the scheduled necropsy. With the exception of discoloured urine due to the colour of the test item, no further treatment-related clinical finding was noted in any dose group. At 50 mg/kg bw/day, slight treatment-related effects were observed on body weight gains and corrected body weight gains. In the other groups, mean body weight, mean body weight gain and mean corrected body weight gain were similar to the control group and not affected by the treatment with the assessed chemical.

There was no treatment-related effect on the relevant reproduction parameters in any dose group and macroscopic examination also did not show any treatment-related adverse effects in any dose group. No treatment-related effects were observed for any foetal parameters including of foetal body weight, sex ratio, external, visceral, skeletal and cartilage abnormalities, and variations or ossification and supernumerary ribs in any dose group.

A NOAEL for maternal and developmental toxicity was established as 50 mg/kg bw/day, based on the absence of treatment related adverse effects up to the highest dose tested.

Carcinogenicity

Cell Transformation Assay in Syrian Hamster Embryo Cells (SHE Assay)

The assessed chemical (purity: 99.88%) has been investigated for the clonal transformation in SHE cells according to the OECD draft guidelines (2012). Under the experimental conditions used, the assessed chemical did not induce morphological transformation of cell colonies and consequently raising the possibility that the assessed chemical is unlikely to be carcinogenic.

Medium-term liver carcinogenesis assay in rats

Male rats Crl:CD (SD) (n=10/dose) were treated by oral gavage doses of the assessed chemical (purity: 99.85%) at 0, 150 and 250 mg/kg bw/day during a 2-week initiation period. For comparison a positive control was used at 600 mg/kg bw/day during a 2-week initiation. Following the 2-week initiation period, rats were given sodium phenobarbital, an established liver tumour promoter, at a dietary level of 500 ppm for 6 weeks, from week 3 to week 8. All animals were subjected to partial hepatectomy after week 3 (one week after starting the sodium phenobarbital treatment) and killed after week 8.

All males survived until the scheduled necropsy (week 8). No signs of discomfort or clinical symptoms, except for colouring of urine at 150 and 250 mg/kg bw/day, from treatment with the assessed chemical were noted. Food and water consumption, gross pathology, relative and absolute liver weight were not affected by the treatment with the assessed chemical.

Under the experimental conditions used, the assessed chemical did not induce glutathione S-transferase placental form (GST-P) positive hepatocyte foci in rats and thus has lack carcinogenesis initiated potential in male rats.

An expert report, as initiated by the SCCS (2016), was also in agreement with the interpretation of the study authors that there was no evidence of increase in GST-P foci in the livers of the study in rats and thus the assessed chemical has no liver carcinogenesis initiating potential in male rats.

Health Hazard Classification

Based on the studies evaluated by the SCCS (2016), the assessed chemical is a hazardous chemical according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia. The hazard classification applicable to the assessed chemical is presented in the following table.

Hazard Classification	*Hazard Statement*
Specific Target Organ Toxicity – Repeated exposure (Category 2)	H373 – May cause damage to organs through prolonged or repeated exposure

6.3. Human Health Risk Characterisation

Based on the studies evaluated by the SCCS (2016), the assessed may cause damage to organs through prolonged or repeated exposure. The assessed chemical is not determined to be a skin sensitiser. A conclusion regarding the skin irritation and eye irritation potentials of the assessed chemical cannot be drawn as the assessed chemical interfered with the assays. However, the assessed chemical is unlikely to be eye and skin irritant at the reduced concentration in end use products (≤ 1.5%).

6.3.1. Occupational Health and Safety

Workers involved in professions where the services provided involve the application of hair dye products containing the assessed chemical to clients (hairdressers and hair salon workers) may be exposed to the assessed chemical at concentrations up to 1.5%. The greatest potential for exposure is during hair dyeing processes, mainly via skin contact, although ocular exposure may also occur. However, as per the applicant, the dye mixture is in a cream form and splashing is unlikely to occur.

Given that the product is a dye, skin contact is expected to be avoided by workers. Workers will use disposable gloves to minimise repeated exposure, and good hygiene practices are expected to be in place.

Overall, based on the low concentration of the assessed chemical in hair dye products and that PPE (gloves) will be worn, the risk to workers from exposure to the assessed chemical is not considered to be unreasonable.

6.3.2. Public Health

Hair dye products containing the assessed chemical will be supplied to professionals (hair dressers or beauty salon workers) only and will not be made available for home use. Therefore, members of the public may potentially be exposed to the assessed chemical only when having the product applied to their scalp (at ≤ 0.5% concentration). The degree and type of exposure may vary depending on the frequency of application, the care taken when applying the dye and amount of dye applied.

Local effects

Irritation or sensitisation effects are not expected from the use of products containing the assessed chemical at the proposed low on-head use concentration (up to 0.5%). Possible use of gloves will further reduce exposure and risk.

Systemic effects from repeated use

The assessed chemical is intended to be used as a component of an oxidative hair dye, and was the subject of a SCCS Opinion (SCCS, 2016), which calculated MoS for the use of the assessed chemical under oxidative conditions as follows. While the following calculation is based on the 1.5% on-head use concentration, the proposed application is for use of the assessed chemical in oxidative hair dye products only at a maximum on-head concentration of ≤ 0.5%.

Absorption through the skin	A	1.35 µg/cm^2
Skin area surface	SAS	580 cm^2
Dermal absorption per treatment	SAS × A × 0.001	0.783 mg
Typical body weight of human		60 kg
Systemic exposure dosage (SED)	SAS × A × 0.001/60	0.013 mg/kg bw
No Observed Adverse Effect Level	NOAEL	3 mg/kg bw/day (derived for sub-chronic toxicity, oral, rat study)
77% bioavailable*		2.31 mg/kg bw/day
MoS	NOAEL/SED	180

*Based on the toxicokinetics study of the assessed chemical.

Based on the 1.5% on-head use concentration, the SCCS (2016) concluded that the use of assessed chemical in oxidative hair dye formulations does not pose a risk to the health of the consumer.

The proposed application is for use of the assessed chemical in oxidative hair dye products at a maximum on-head concentration of ≤ 0.5% that is less than that was assessed by the SCCS (2016). Therefore, systemic repeated dose risks from the use of the assessed chemical by members of the general public at ≤ 0.5% on-head concentration in oxidative hair dyes 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 assessed chemical will not be manufactured, reformulated or repacked in Australia. It will be imported as a component of finished hair dye products. Some release of the assessed chemical may be from spills during the transport and storage of the finished products containing the assessed chemical. Accidental spills will be collected for disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The majority of the assessed chemical will be rinsed into the sewer system as a result of its use in hair dye products.

RELEASE OF CHEMICAL FROM DISPOSAL

Residues of the assessed chemical in empty product containers are likely to either share the fate of the containers and be disposed of to landfill or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

The majority of the assessed chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis.

A proportion of the assessed chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill as a waste (see Predicted Environmental Concentration). Minor amounts of the assessed chemical may also be disposed of to landfill as collected spills and empty container residues. The assessed chemical residues in landfill and soils are expected to have low mobility based on its estimated soil adsorption coefficient (log Koc = 3.91). The assessed chemical is not expected to bioaccumulate based on the estimated moderate partition coefficient (log Pow = 3.6). In the aquatic and soil compartments, the assessed chemical is expected to degrade through biotic and abiotic processes to form water and oxides of carbon, nitrogen, sulphur and chlorine.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the assessed chemical being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 100% release of the assessed chemical into sewer systems nationwide over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in sewage treatment processes (STP) based on the properties of the assessed chemical has not been considered for this scenario, and therefore no removal of the assessed chemical during STP is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	70	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	70	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	0.19	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10.0	
PEC - River:	0.04	µg/L
PEC - Ocean:	0.00	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The assessed chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.04 µg/L may potentially result in a soil concentration of approximately 0.00026 mg/kg. Assuming accumulation of the assessed chemical in soil for 5 and 10 years under repeated irrigation, the concentration of assessed chemical in the applied soil in 5 and 10 years may be approximately 0.0013 mg/kg and 0.0026 mg/kg, respectively.

7.2. Environmental Effects Assessment

Ecotoxicity studies on the assessed chemical were not submitted and are not required for limited notifications.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) has not been calculated as ecotoxicity studies were not available.

7.3 Environmental Risk Assessment

A risk quotient (PEC/PNEC) for the assessed chemical was not calculated as ecotoxicity data were not available. The assessed chemical is unlikely to reach ecotoxicologically significant concentrations in the environment based on its annual importation quantity and use pattern. On the basis of the low import volume, the assessed chemical is not considered to pose an unreasonable risk to the environment.

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