1,4-Benzenediamine, 2-nitro-N1-phenyl-: Human health tier II assessment

02 March 2018

CAS Number: 2784-89-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

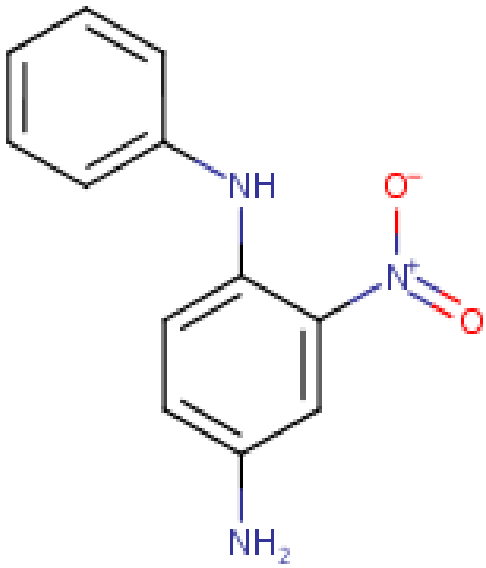
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-nitro-4-aminodiphenylamine HC Red no 1 1-anilino-4-amino-2-nitrobenzene 2-nitro-N-phenylbenzene-1,4-diamine p-phenylenediamine, 2-nitro-N1-phenyl-
Structural Formula	
Molecular Formula	C12H11N3O2
Molecular Weight (g/mol)	229.24
Appearance and Odour (where available)	green brown crystalline powder
SMILES	c1(Nc2ccccc2)c(N(=O)=O)cc(N)cc1

Import, Manufacture and Use

Australian

The chemical has been reported to be used as a hair dye in Australia (NICNAS, 2007).

International

The following international uses have been identified through the European Chemicals Agency (ECHA) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database; eChemPortal; Galleria Chemica; Health Canada Cosmetic Ingredient Hotlist; New Zealand Inventory of Chemicals (NZIoC); Substances and Preparations in the Nordic countries (SPIN) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the US Department of Health and Human Services Household Products Database (US HPD).

The chemical is used as a hair dye substance or colourant in non-oxidative (semi-permanent) hair dye products with a reported intended maximum on-head concentration of 1.0 % in the EU (SCCP, 2006) and 0.5 % in the US (CIR, 1996; CIR, 2017). The chemical is restricted for use in a number of countries (see **Restrictions: International** section).

The chemical was used in 36 cosmetic products in the US in 2011 (Personal Care Products Council, 2011), while in 2017 it has been listed in only two products (Environmental Working Group (EWG)).

Restrictions

Australian

The chemical is not separately listed in the *Poisons Standard — the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2018). However, since the chemical is an N-arylated nitro derivative of phenylenediamine, the chemical group restrictions for ‘PHENYLENEDIAMINES’ contained in Schedules 6 and 10 of the SUSMP apply to the chemical (SUSMP, February 2018).

Schedule 6:

'PHENYLENEDIAMINES including alkylated, arylated and nitro derivatives not elsewhere specified in these Schedules:

a) in preparations packed and labelled for photographic purposes;

b) in preparations packed and labelled for testing water except tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, “Do not discard testing solutions into the pool”;

c) in hair dye preparations except when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING — This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING — This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.'

Schedule 6 chemicals are labelled 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label (SUSMP, February 2018).

Schedule 10:

'PHENYLENEDIAMINES, including alkylated, arylated and nitro derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows except when included in Schedule 6'.

Schedule 10 chemicals are 'substances of such danger to health as to warrant prohibition of sale, supply and use — substances which are prohibited for the purpose or purposes listed for each poison' (SUSMP, February 2018).

International

The use of the chemical in non-oxidative hair dye products is restricted by the Association of Southeast Asian Nations (ASEAN) and the EU as a ‘substance which cosmetic products must not contain except subject to restrictions laid down’ in the following (Galleria Chemica):

- the EU Council Directive 2012/21/EU - Annex III/I/270; and
- the ASEAN Cosmetic Directive Annex III.

The restrictions include:

- maximum concentration in ready for use (non-oxidative) preparations of 1.0%; and
- conditions of use and warning to be printed on the label: 'Hair colorants can cause severe allergic reactions. Read and follow instructions. This product is not intended for use on persons under the age of 16. Temporary “black henna” tattoos may increase your risk of allergy. Do not colour your hair if: — you have a rash on your face or sensitive, irritated and damaged scalp, — you have ever experienced any reaction after colouring your hair, — you have experienced a reaction to a temporary “black henna” tattoo in the past.’

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

Based on available data, the chemical is expected to be poorly absorbed (less than 2 %) through the skin when used in hair dye formulations.

Percutaneous absorption of the chemical at 1 % (in a non-oxidative hair dye formulation base) through human skin, 48 hours following a 30-minute exposure period was determined in the following in vitro studies:

- OECD Test Guideline (TG) 428 study (SCCP, 2006) — maximum total absorption of 0.7 %. About 0.1 % remained bound to the outer most layer of skin (stratum corneum); and
- non-guideline study (CIR, 1996) — total absorption of 1.68 %. The rate of percutaneous absorption was found to be linear for the first 4 hours following exposure and then reducing to almost zero by 24 hours.

Acute Toxicity

Oral

The chemical has moderate acute toxicity following oral exposure with a median lethal dose (LD50) between 625–1250 mg/kg bw in female rats, warranting hazard classification (see **Recommendation** section).

In a non-guideline acute toxicity study in Sprague Dawley (SD) rats, the oral LD50 of the chemical was between 625–1250 mg/kg bw in females and 2500–5000 mg/kg bw in males (CIR, 1996; SCCP, 2006).

A non-guideline study reported an oral LD50 of 1250 mg/kg bw in rats (Registry of Toxic Effects of Chemical Substances (RTECS)). No other study details are available.

Dermal

No data are available. Whilst the chemical has moderate acute toxicity following oral exposure, it is expected to have poor dermal absorption (less than 2 %) when used in hair dye formulations. Based on data from a structurally similar chemical (analogue) with similar acute oral toxicity, 1,4-benzenediamine, N-phenyl (CAS No. 101-54-2), the chemical is expected to have low acute dermal toxicity (NICNASa).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is not expected to be irritating to skin based on the limited data available.

In a primary irritation test in rabbits (n=6), the chemical (500 mg) applied as an aqueous slurry to shaved intact skin without occlusion, did not cause signs of irritation up to 72 hours after application (CIR, 1996; SCCP, 2006).

Eye Irritation

Based on the limited data available, the undiluted chemical is mildly irritating to eyes. The reported transient effects do not warrant hazard classification.

In a non-guideline ocular irritation study, the undiluted chemical applied directly to eyes (conjunctival sac) of rabbits (n=4) produced the following irritation effects (measured with modified Draize scoring) in all animals post-treatment (CIR, 1996; SCCP, 2006):

- deep conjunctival redness (grade 2 of 3) at 1 hour;
- conjunctival redness (grade 1 of 3) at day 1 (and 1 animal at day 2); and
- eyelid swelling (chemosis) (grade 1 of 4) at 1 hour, day 1 and 2.

Treated eyes appeared normal by day 3 (CIR, 1996).

In a standard Draize test, the undiluted chemical was reported to be mildly irritating to rabbit eyes (RTECS). No other study details are available.

Sensitisation

Skin Sensitisation

The chemical is a strong sensitiser based on available data, warranting hazard classification (see **Recommendation** section).

In a maximisation test, 10 female Hartley albino guinea pigs were treated with 0.1 % chemical (in propylene glycol) for intradermal induction and 25 % chemical for topical induction. Prior to topical induction, pre-treatment with sodium lauryl sulfate (SLS) was performed. Both on challenge at 5 % and re-challenge at 2 %, the chemical (in propylene glycol) produced a positive dermal response in 10/10 animals (CIR, 1996; SCCP, 2006).

In an open epicutaneous test (OET) performed with only a single induction and challenge dose, 3 % chemical in vehicle (isopropanol/Tween/hydroxyethyl cellulose/sodium sulfide) produced a positive dermal response in 7/10 and 4/10 female Hartley albino guinea pigs 48 and 72 hours after challenge, respectively (CIR, 1996; SCCP, 2006; Kimber et.al, 2011). The dermal response included erythema (redness) but no oedema (swelling).

In a photosensitisation study, the chemical produced a contact allergic reaction but not a photoallergic reaction in guinea pigs (CIR, 1996) . Hartley albino guinea pigs (n=8/sex/group) were treated with 10 % chemical in vehicle (dimethylacetamide/acetone/ethanol) for topical induction along with intradermal injection of Freund's complete adjuvant (FCA). Application sites were treated with UVA and UVB in stages. No irritation was seen during induction at the chemical application sites. Upon challenge with 5 % chemical in vehicle, 13/16 animals showed consistent positive dermal response at all challenge sites (with and without irradiation). Re-challenge with 0.1 % chemical without irradiation produced responses in 7/16 animals.

Equivocal results were seen in two independent, non-standard local lymph node assays (LLNA) (SCCP, 2006). The chemical was tested at doses of 0.25, 0.5, 1 and 2 % in dimethyl sulfoxide (DMSO). The following stimulation indexes (SI) were produced in the two studies:

- study 1: 0.35 (0.25 %), 1.06 (0.5 %), 1.04 (1.0 %) and 1.52 (2.0 %); and
- study 2: 3.49 (0.25 %), 1.73 (0.5 %), 1.51 (1.0 %) and 4.27 (2.0 %).

The conditions of study 1 are questionable due to the poor performance of the positive control. The chemical induced skin sensitisation in study 2. However, the SCCP stated that the highest test concentration was too low and not in accordance with the requirements of the standard test guidelines for both studies (SCCP, 2006).

Observation in humans

The chemical was a skin sensitiser in one human repeat insult patch test (HRIPT).

In a HRIPT study (n=103, mostly females), the chemical applied as a 3 % slurry with occlusion induced the following reactions (CIR, 1996; SCCP, 2006):

- during 1–9 day induction — strong positive reactions (definite erythema, definite oedema and vesiculation) (n=1), which may be indicative of pre-sensitisation; doubtful responses (barely perceptible erythema) (n = 66–98); and
- on challenge — strong positive reactions (n=1 after 48 hours, n=2 after 72 hours); doubtful responses (n=27 after 48 hours, n=37 after 72 hours).

Repeated Dose Toxicity

Oral

Data available indicate that the chemical may induce some degree of haematotoxicity following repeat oral exposure.

In a 90-day oral toxicity study (OECD TG 408), the chemical (2, 5 or 20 mg/kg bw/day) produced the following treatment-related adverse effects in SD rats (SCCP, 2006):

- haematology — increased mean corpuscular haemoglobin (MCH) in males at 20 mg/kg bw, increased white blood cells (leukocytes) and lymphocytes in females at 5 mg/kg bw (statistically significant) and 20 mg/kg bw, statistically significant decrease in red blood cells (erythrocytes) in females at 20 mg/kg bw; and
- organ weights — statistically significant decrease in thymus weight in males at 20 mg/kg bw and pituitary weight in females in 5 mg/kg bw dose group only.

Dose-related orange coloured urine and staining of the body were not considered adverse. The SCCP considered a no observed adverse effect level (NOAEL) of 5 mg/kg bw/day (SCCP, 2006). However, due to the significant haematological changes seen in females at the 5 mg/kg bw/day dose group, the NOAEL should be considered to be 2 mg/kg bw/day. In the accompanying 14-day dose finding study (dose groups 0, 50, 150, 300 or 600 mg/kg bw/day), notable adverse effects seen in both males (from 300 mg/kg bw) and females (from 150 mg/kg bw) included decreased red blood cells and increased MCH, mean haemoglobin, polychromatic red blood cells (immature cells), alanine aminotransferase and total bilirubin. These effects were suggestive of bone marrow or regenerative response to haemolytic anaemia (Haschek & Rousseaux, 1991; SCCP, 2006). Increases in liver and spleen weights were also seen in both sexes.

In a non-guideline 90-day oral toxicity study in SD rats (fed 0.01, 0.03 or 0.1 % chemical in diet, approximating to doses of 9, 27 and 90 mg/kg bw/day), an increase in pigment composed mainly of haemosiderin (a breakdown product of red blood cells) was noted in the spleen of females in the mid and high dose groups (CIR, 1996; EFSA, 2012). However, the only significant haematological change seen was an increase in percentage of neutrophils (type of white blood cell) in females in the highest dose group. Other significant changes included increase in bilirubin (females only), and serum triglycerides and blood urea nitrogen (males only) in the highest dose group. There were two animal deaths, one female in the mid-dose group and one male in the highest dose group. Necroscopy results of these two animals showed no significant chemical-related changes except for dark areas in lungs, liver, spleen, stomach and/or kidneys. In the accompanying 14-day dose finding study, SD rats on a chemical diet (feed concentrations 0.05, 0.1, 0.2, 0.4, 0.6 and 0.8 %, approximating to 60, 120, 240, 480, 720 and 960 mg/kg bw/day) showed increases in liver, kidney and spleen weights (CIR, 1996; EFSA, 2012). Chemical-induced lesions were seen in the liver (females in the highest dose group only) and spleen (females dosed at 240 and 960 mg/kg bw and less prominently in males at 120 mg/kg bw).

A structurally similar chemical (analogue), 1,4-benzenediamine, N-phenyl (CAS No. 101-54-2) produced similar haematological changes and degeneration of the liver in male Wistar rats, in a non-guideline oral repeat dose toxicity study at doses of 250 and 375 mg/kg bw/day (SCCPa, 2006; EFSA, 2012). The haematological changes, which included a decrease in red blood cells and haemoglobin, and an increase in mean corpuscular volume (MCV) were suggestive of normocytic normochromic anaemia (SCCPa, 2006).

Dermal

The chemical is not expected to cause serious damage to health following repeat dermal exposure based on data available on complex hair dye formulations containing the chemical. There is some evidence of haematotoxicity, consistent with repeat dose toxicity following oral exposure.

In a non-guideline multi-generational study in SD rats (CIR, 1996; SCCP, 2006), the first generation (F1) received topical treatment of a semi-permanent hair dye formulation containing the chemical at 0.15 % (along with 12 other hair dye substances) from the time of their weaning to the weaning of their offspring. The second generation (F2) received the same topical treatment as F1 for 2 years (some animals were sacrificed and necropsied after 12 months of treatment). The following biologically significant adverse effects were seen in F2, which may potentially be treatment-related:

- incidence of haematopoiesis (formation of blood cells) in the liver, which was somewhat higher than the controls;
- cellular proliferation or hyperplasia of the parathyroid gland and liver;
- thickening of outer layer of skin (hyperkeratosis) and allergic skin reaction (dermatitis); and
- sialadenitis (infection of salivary glands).

The study is of supportive value only due to the complexity of the test material.

The following two independent studies were performed with a semi-permanent hair dye formulation (containing the chemical at 0.15 % along with 12 other hair dye substances) in different species (CIR, 1996; SCCP, 2006):

- a non-guideline 90-day dermal toxicity study in rabbits — a significant increase in white blood cells (females only) and blood urea nitrogen (BUN) (in both sexes) was seen (Burnett et al., 1976); and
- a non-guideline 23-month topical study in Swiss Webster mice — no significant adverse effects were seen in either sex (Burnett et al., 1980).

These studies are of limited value due to the complexity of the test material.

Inhalation

No data are available.

Genotoxicity

The chemical is not considered to be genotoxic based on available data. While the chemical was positive for genotoxicity in one in vitro test, the positive results were not confirmed in vivo.

The following in vitro data are available (CIR, 1996; SCCP, 2006):

In a chromosomal aberration test in Chinese hamster ovary (CHO) cells, the chemical (20–100 µg/mL without metabolic activation; 50–120 µg/mL with metabolic activation) produced a concentration-dependent, statistically significant increase in the number of cells with chromosomal aberrations (aneuploid cells) in the presence of metabolic activation. No significant increase was seen in the frequency of cells with a numerical change in whole set of chromosomes (polyploid cells). Similar results were seen in two independent non-guideline chromosomal aberrations studies in CHO cells.

The chemical tested negative for genotoxicity in the following:

- bacterial gene mutation test (OECD TG 471) in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 *uvr*A (2.5–5000 µg/plate), with and without metabolic activation;
- two independent Ames tests in *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538, with (up to 5000 µg/plate) and without (up to 1000 µg/plate) metabolic activation;
- mouse lymphoma assay (tk locus) (OECD TG 476) (5–30 µg/mL and 1.5–140 µg/mL with and without metabolic activation, respectively); and
- unscheduled DNA synthesis (OECD TG 482) in primary rat hepatocytes (1–25 µg/mL).

The following in vivo data are available (CIR, 1996; SCCP, 2006):

In a mammalian erythrocyte micronucleus test (OECD TG 474), the chemical did not induce an increase in micronuclei in the bone marrow of male mice dosed up to 2000 mg/kg bw.

Carcinogenicity

Carcinogenicity of the chemical cannot be inferred from the very limited data available.

Two non-guideline dermal studies performed with a semi-permanent hair dye formulation containing the chemical at 0.15 % along with 12 other hair dye substances (see **Repeated dose toxicity: Dermal** section) produced the following results (CIR, 1996; SCCP, 2006):

- multi-generational study in SD rats — cellular proliferation or hyperplasia of the parathyroid gland and liver was seen in the second generation of treated animals. There was no difference in tumour incidence between test and control populations; and
- dermal study in Swiss Webster mice — there was no significant increase in tumours relative to controls (Burnett et al., 1980).

These studies are of supportive value only due to complexity of the test material.

A structurally similar chemical (analogue), 1,4-benzenediamine, N-phenyl (CAS No. 101-54-2) was not carcinogenic in Fischer 344 rats and B6C3F1 mice in a National Toxicology Program (NTP) bioassay (NTP, 1978). The following were the test doses (NTP, 1798; EFSA, 2012):

- rats (n=50/sex/dose) — fed 600 or 1200 ppm chemical diet (approximately 30 and 60 mg/kg bw/day, respectively) for 78 weeks and observed for a further 26 weeks (total study period = 104 weeks); and
- mice (n=50/sex/dose) — fed a time-weighted average chemical diet of 2057 or 4114 ppm in males (approx. 300 and 615 mg/kg bw/day) and 3672 or 8170 ppm (approx. 555 and 1230 mg/kg bw/day) in females for 48 weeks and observed for a further 43 weeks (total=91 weeks).

The mean body weights were lower in both rats and mice compared with the controls. Mortality rates were higher in mice (especially females) before decreasing the test doses. The shortened treatment time in mice may have precluded their use in the study (NTP, 1978). There were no significant differences in the incidence of neoplasms between test and control populations in both species.

Reproductive and Developmental Toxicity

The chemical is not expected to have specific reproductive or developmental toxicity based on available data.

In a prenatal developmental toxicity study (OECD TG 414) in Charles River (CD) rats, no treatment-related adverse effects were seen in litter parameters and foetal development (SCCP, 2006). The chemical was administered via oral gavage to pregnant female rats at 0, 25, 75 or 125 mg/kg bw/day on gestation days (GD) 6–20. The only significant adverse effect observed was a

reduction in maternal body weight (accompanied by reduction in feed consumption) in all dosed animals. The study showed a maternal NOAEL of 25 mg/kg bw/day and a developmental NOAEL of 125 mg/kg bw/day.

A non-guideline developmental toxicity study in female SD rats, the chemical (at 0.01, 0.03 or 0.1 % in diet, approximating to doses 9, 27 and 90 mg/kg bw/day, respectively) dosed for 15 weeks prior to mating did not adversely effect foetal development (CIR, 1996; EFSA, 2012).

In a non-guideline teratogenicity study, topical application of a semi-permanent hair dye formulation containing the chemical at 0.15 % (along with 12 other hair dye substances) every third day during GD 1–19 produced no embryonic or teratogenic effects in CD rats (Burnett et al., 1976; CIR, 1996).

In a non-guideline dermal multi-generational study in SD rats (see **Repeated dose toxicity: Dermal** section), the chemical did not adversely effect fertility, gestation and live birth indexes in three generations of treated animals. The study is of supportive value only due to the complexity of the test material.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation. The chemical may also be harmful on ingestion at high doses.

The chemical is a secondary amine and thus prone to nitrosation and formation of carcinogenic N-nitroso-compounds (NOCs) under nitrosating conditions (SCCS, 2012).

Public Risk Characterisation

The chemical is reported to be used in hair dyes in Australia and overseas.

The ASEAN and the EU have restricted the use of the chemical in cosmetics. In Australia, the chemical is regulated through its inclusion in the 'PHENYLENEDIAMINES' chemical group of the SUSMP. The 'PHENYLENEDIAMINES' are listed on Schedules 6 and 10 of the SUSMP with restrictions and/or prohibitions on their use in specific cosmetic products. The Schedule 6 entry in the SUSMP allows phenylenediamines to be included in hair dye preparations and in eyelash and eyebrow tinting products, provided the label includes warning statements regarding skin and eye irritation. Current controls are considered adequate to minimise the risk to public health posed by hair dyes containing the chemical.

Occupational Risk Characterisation

Given the critical systemic long-term and acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral and dermal exposure are implemented. Oral and dermal exposure can be prevented by good hygiene practices. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient provided that the existing risk management is implemented, recommended amendments to the classification are adopted, and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, February 2018).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1A (H317)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral and dermal exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;

- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

Bailey, JE (ed.) 2011. Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 1st Edition, Personal Care Products Council, Washington, D.C.

Burnett C, Goldenthal E, Harris S, Wazeter F, Strausburg J, Kapp R and Voelker R, 1976. Teratology and percutaneous toxicity studies on hair dyes. J Toxicol Environ Health. 1(6), 1027-40.

Burnett C, Jacobs M, Seppala A and Shubik P, 1980. Evaluation of the toxicity and carcinogenicity of hair dyes. J Toxicol Environ Health. 6(2), 247-257.

Cosmetic Ingredient Review Expert Panel (CIR, 1996). Final report on the safety assessment of HC Red No. 1. Accessed at http://gov.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr12.pdf

Cosmetic Ingredient Review Expert Panel (CIR, 2017). 40th Anniversary overview and rereview summaries from 2011 to 2015. HC Red No. 1. Accessed at http://gov.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR758.pdf

Cosmetic Ingredients& Substances (CosIng) Database. European Commission. Accessed November 2017 at http://ec.europa.eu/consumers/cosmetics/cosing/

eChemPortal. Accessed November 2017 at http://www.echemportal.org/echemportal/substancesearch/substancesearchlink.action

Environmental Working Group (EWG). Skin Deep Cosmetics Database. Accessed November 2017 at http://www.ewg.org/skindeep/

European Chemicals Agency (ECHA). Chemical Information. Accessed November 2017 at https://echa.europa.eu/

European Food Safety Authority (EFSA) 2012. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal, 10(3): 2579 (32 pp.).

Galleria Chemica. Accessed November 2017 at http://jr.chemwatch.net/galeria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Haschek W and Rousseaux C 1991. Handbook of toxicologic pathology. Academic Press, Inc., San Diego, California, pp. 389-414.

Hazardous Substances Data Bank (HSDB). Accessed November 2017 at http://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm

Health Canada. Cosmetic Ingredient Hotlist – Prohibited and Restricted Ingredients. Ottawa: Health Canada. Accessed November 2017 at http://www.hc-sc.gc.ca/cps-spc/cosmet-person/hot-list-critique/index-eng.php

Kimber I, Basketter DA, Berthold K, Butler M, Garrigue J-L, Lea L, Newsome C, Roggeband R, Steiling W, Stropp G, Waterman S, Wiemann C, 2001. Skin sensitization testing in potency and risk assessment. Toxicol Sci. 59(2), 198–208.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2007. List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia. Unpublished internal document.

National Toxicology Program (NTP) 1978. Techinical report series no. 82 - Bioassay of N-phenyl-p-phenylenediamine for possible carcinogenicity (CAS No. 101-54-2). U.S. Department of Health and Human Services. Accessed December 2017 at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr082.pdf

New Zealand Environmental Protection Authority Inventory of Chemicals (NZIoC). Accessed November 2017 at http://www.epa.govt.nz/search-databases/Pages/nzioc-search.aspx

NICNASa. Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for 1,4-benzenediamine, N-phenyl (CAS No. 101-54-2). Available at http://www.nicnas.gov.au

Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed November 2017 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

Registry of Toxic Effects of Chemical Substances (RTECS). 1,4-Benzenediamine, 2-nitro-N(sup 1)-phenyl- (CAS No. 2784-89-6). Accessed November 2017 at http://ccinfoweb.ccohs.ca/rtecs/search.html

Safe Work Australia. Hazardous Chemicals Information System (HCIS). Accessed November 2017 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

Scientific Committee on Consumer Products (SCCP) 2004. Opinion on HC Red n° 1, COLIPA N° B48. SCCP/0981/06. Adopted at the 9th plenary meeting of 10 October 2006. Available at http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_072.pdf

Scientific Committee on Consumer Products (SCCPa) 2004. Opinion on N-phenyl-p-phenylenediamine, COLIPA N° A9. SCCP/0991/06. Adopted at the 10th plenary meeting of 19 December 2006. Available at https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_089.pdf

Scientific Committee on Consumer Safety (SCCS) 2012. Opinion on nitrosamines and secondary amines in cosmetic products. Adopted at its 4th plenary meeting of 27 March 2012. Available at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_090.pdf

The Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database. Accessed November 2017 at http://webnet.oecd.org/hpv/ui/Search.aspx

The Poisons Standard, February 2018. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 19. Accessed at https://www.legislation.gov.au/Details/F2018L00043

US Department of Health and Human Services, Household Products Database (HPD). Accessed November 2017 at https://hpd.nlm.nih.gov/advancedsearch.htm

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