Ethanol, 2-[(2-nitrophenyl)amino]-: Human health tier II assessment

30 June 2017

CAS Number: 4926-55-0

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.

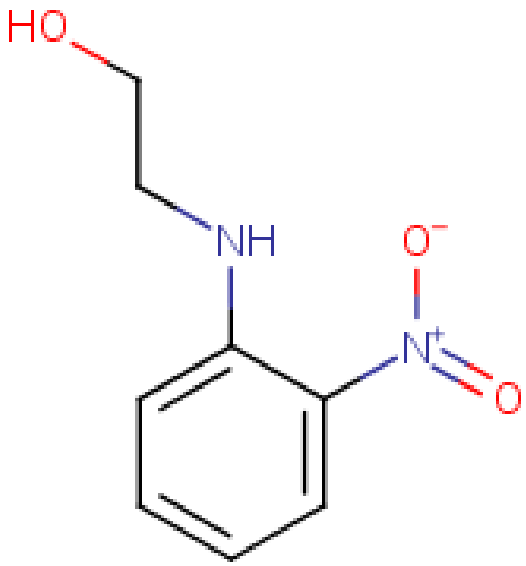
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-nitro-N-(2-hydroxyethyl)aniline HC Yellow No. 2 N-(2-hydroxyethyl)-2-nitroaniline 2-((2-nitrophenyl)amino)ethanol ethanol, 2-(o-nitroanilino)- (8CI)
Structural Formula	
Molecular Formula	C8H10N2O3
Molecular Weight (g/mol)	182.2
Appearance and Odour (where available)	Fine orange powder.
SMILES	c1(NCCO)c(N(=O)=O)cccc1

Import, Manufacture and Use

Australian

The chemical is on the ‘List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia’ (NICNAS, 2007).

International

The chemical is listed as a hair dye substance in oxidative and non-oxidative hair dye products in the European Commission Cosmetic Ingredients and Substances (CosIng) database and as a hair colourant in the United States (US) Personal Care Product Council International Cosmetic Ingredients (INCI) Directory and the US Department of Health and Human Services Household Products Database (US HPD).

The only reported use of the chemical is in hair dyes/colours and hair rinses (CIR, 1994). The chemical is used in 188 cosmetic products in the US (Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 2011). Use concentrations up to 1 % have been reported (CIR,1994, SCCS, 2010).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed in the European Union (EU) Cosmetic Directive 76/768/EEC Annex III: List of Substances which cosmetic products must not contain except subject to the restrictions and conditions laid down. This includes the following restrictions:

- for non-oxidative hair dye products, the maximum concentration in ready to use preparation is 1.0 %;
- for oxidative hair dye products, the maximum concentration applied to hair after mixing in oxidative conditions is 0.75 %;
- do not use with nitrosating agents;
- maximum nitrosamine content is 50 µg/kg;
- keep in nitrite-free containers; and
- to be printed on the label: hair colourants can cause allergic reactions.

The chemical is registered on the New Zealand Inventory of Chemicals (NZIoC) for possible use as a component in a product covered by a group standard but is not approved for use as a chemical in its own right.

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 (Galleria Chemica).

Health Hazard Information

Toxicokinetics

Only limited information is available. The chemical is expected to have poor dermal absorption when used in hair dye formulations.

Data from dermal/percutaneous absorption study (human skin, non-oxidative conditions) (Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 428) indicate that the penetration of the chemical through human skin is slow. Under non-oxidative conditions, the dermal absorption of a hair dye formulation containing 1% of the chemical (30 minute contact period) was 4.02 ± 1.29 µg/cm^2 (2.01 ± 0.64 % of the applied dose) after 48 hours (SCCS, 2010).

A similar study on pig skin under oxidative conditions (OECD TG 428) showed that the dermal absorption of a hair dye formulation containing the chemical at 1.5 % (30 minute contact period) was 6.06 ± 2.21 µg/cm² (4.71 ± 1.70 % of the applied dose) after 24 hours (SCCS, 2010).

No other toxicokinetics data are available.

Acute Toxicity

Oral

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

In a non-guideline toxicity study (SCCS, 2010), the chemical was administered via oral gavage to Sprague Dawley (SD) rats (n = 5/sex) at dose levels 625, 1250 and 2500 mg/kg bw. No effects were observed at the low dose. More than half the females died at 1250 mg/kg bw, while no deaths were observed in the males. At 2500 mg/kg bw all the rats died. No data are available on the signs of toxicity. Based on the results, 1250 mg/kg bw is taken as a safe approximation of LD50.

Dermal

No data are available. Based on the limited expected dermal absorption the chemical is expected to have low acute dermal toxicity.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data the chemical is considered to be at most a slight skin irritant, not warranting classification.

In a non-guideline study, 500 mg of the chemical was applied as aqueous slurry under non-occluded conditions to the intact skin of six New Zealand White (NZW) rabbits and left in contact for 24 hours (CIR, 1994; SCCS, 2010). Sites were scored for dermal irritation at 24 and 72 hours post-application according to the Draize method. No apparent dermal irritation was observed (SCCS, 2010).

Eye Irritation

Based on the available data, the chemical is considered to be a mild eye irritant, not warranting classification.

In a non-guideline study, the chemical was found to produce ocular irritation when applied as a powder (100 mg) directly to the left conjunctival sac of four NZW rabbits (CIR, 1994; SCCS, 2010). The eyes of two of the rabbits were rinsed with distilled water after treatment. All eyes were examined and scored one hour and one, two and three days post-treatment according to the Draize method. Conjunctival redness, swelling, and discharge were observed in the eyes of all animals when examined one hour after treatment. Low grade corneal opacity with ulceration was noted in three of four rabbits at day one; one animal exhibited irritation of the iris. Whilst data on the mean scores are not available, by day two, most conjunctival and iris effects were reduced or absent and corneal opacity in the one rabbit had cleared. All effects were reversed within three days. Overall, the eyes rinsed with distilled water after treatment appeared to be less irritated than those not rinsed. The study concluded that the chemical is irritating to eyes.

In the same non-guideline study, conducted with the chemical instilled as a 10 % aqueous suspension produced slight conjunctival responses in the eyes of all four NZW rabbits (rinsed and un-rinsed) when examined one hour after instillation (CIR, 1994; SCCS, 2010). The effects were reversed within two days. The study concluded that the chemical is slightly irritating to eyes.

Observation in humans

In one HRIPT study intended to evaluate sensitisation potential of the chemical (see **Skin sensitisation** section for study details), two of the 98 test subjects reported slight erythematous reactions to the chemical at 3 %, which upon testing were considered to be ‘due to irritation and not sensitisation’ (CIR, 1994; SCCS, 2010).

Sensitisation

Skin Sensitisation

Data from animal testing and two HRIPT studies (n = 100/study) indicate that the chemical may not be a skin sensitiser. However, it is noted that the SCCS does not exclude a possible sensitising potential of the chemical.

In a non-guideline local lymph node assay (LLNA) in CBA female mice, the chemical was not found to induce sensitisation (SCCS, 2010). Female mice (n = 5/group) were topically exposed to the chemical at concentrations of 0, 0.25, 0.5, 1 or 2 % for three consecutive days. Stimulation indexes (SI) were 1.19, 0.79, 1.03 and 1.28 for the respective concentrations, indicating that

the chemical did not induce lymphocyte proliferation at concentrations up to 2 %. However, sensitising potential cannot be excluded based on this study since the concentrations tested were too low (SCCS, 2010).

In a guinea pig maximisation test (GPMT), female Hartley albino guinea pigs (n = 10/group) were intradermally induced with the chemical at 1 %. One week after the induction, the guinea pigs were topically induced with the chemical at 25 % under an occlusive patch for 48 hours. Two weeks later, the guinea pigs were challenged with a single topical application of the chemical at 3 %. No skin reactions were observed at challenge (SCCS, 2010).

In a non-guideline photosensitisation study, the chemical at 10 % tested negative in Hartley albino guinea pigs (n = 8/sex) (CIR, 1994). During the first week of induction, the guinea pigs were dermally induced with the chemical at 10 %, on a shaved and depilated nuchal area, one hour before being irradiated, for four consecutive days. The same procedure was conducted on the second and third week of induction, after injection of Freund's complete adjuvant (FCA). Two weeks after the end of induction, the guinea pigs were challenged with dermal application of the chemical at 5 % on the left lumbar area. No irritation was observed during the induction phase and no reactions indicative of 'chemical-induced sensitisation or photosensitisation' were observed (CIR, 1994) at challenge.

The related chemical, 2-nitroaniline (CAS No. 88-74-4) was also reported to be negative in a GPMT (OECD, 2004).

Observation in humans

The chemical was tested at 3% in a HRIPT study, which reported slight erythematous reactions in two of the 98 test subjects (CIR, 1994; SCCS, 2010). The study, conducted over a six week period consisted of induction, test and challenge phases. The induction phase involved nine consecutive applications of 3 % chemical in vehicle (12 % isopropanol, 2 % Tween-80, 2 % Natrosol, 0.05 % sodium sulphite, water). The patches were removed 24 hours after application and evaluated every 48 hours. The challenge phase was initiated during week six of the study, with identical patches applied to sites on the opposite arm previously unexposed to the test material. Patches were removed after 24 hours. The sites were graded 24 and 48 hours after removal. Two subjects developed reactions on challenge and were re-challenged. After further testing, the reactions were considered to be due to ‘irritation but not sensitisation’ (CIR, 1994; SCCS, 2010).

In a second HRIPT study performed exactly as the previous study but with a different group of test subjects, one of the 104 test subjects developed definite erythema and oedema during both the induction and challenge phases (CIR, 1994; SCCS, 2010). ‘These responses were interpreted as evidence of pre-sensitisation probably to the vehicle’ (SCCS, 2010).

Repeated Dose Toxicity

Oral

Data from sub-chronic (90 days) and chronic (6 months) toxicity studies, and the reported no observed adverse effect level (NOAEL) of 50 mg/kg bw/day in rats for oral administration indicate that the chemical may cause general systemic toxicity on repeated oral exposure at high doses (from 360 mg/kg bw/day).

In a 90-day toxicity study (OECD 408), administration of the chemical up to 50 mg/kg bw/day via oral gavage in SD rats produced no mortality or notable signs of systemic toxicity or significant histopathological changes (SCCS, 2010). Statistically significant changes in albumin, calcium, phosphorus and chloride were observed in females of all the dosed groups (5, 20 and 50 mg/kg bw/day); however, the changes were not dose related. Furthermore, in the absence of any corresponding changes in kidney weights, renal histopathology or urinalysis parameters these findings were not considered to be adverse effects. A statistically significant decrease in sperm motility was observed in males at 20 and 50 mg/kg bw/day; however, it was not dose-related. Furthermore, no effects on sperm were reported at end of the recovery period and, hence this finding was not considered to be an adverse effect. The study reported a NOAEL of 50 mg/kg bw/day.

In non-guideline sub-chronic (90 days) and chronic (6 months) feeding studies, the chemical at concentrations from 0.4 % (equivalent to 360 mg/kg bw/ day) produced significant changes in various organ sizes and clinical parameters; and reduced body weight gain in rats (CIR, 1994). The sub-chronic study (90 days) was performed on SD rats in four treatment groups (0 %, 0.125 %, 0.4 %, 1.25 % chemical in feed, respectively) (n = 40 males/group, 45–55 females/group). The dose values can be approximated to 112.5, 360 and 1125 mg/kg bw/day, respectively (EFSA, 2012). The chronic study used 10 rats from each of

the sub-chronic study groups and maintained them on their initial diets for an additional 90 days. Except for a small increase in pigment in the spleen, no significant histopathological or haematological changes were observed in any of the dosed groups. However, the following significant clinical changes were observed in both the studies:

- increase in total protein, albumin and calcium (all the dosed groups);
- increase in albumin/globulin ratio, cholesterol (at 0.4 % and 1.25 %);
- increase in methaemoglobin (males dosed at 1.25 %);
- increase in the absolute and relative weights of liver, thyroid gland, brain, kidney, adrenal gland and heart (from 0.4 %); and
- decrease in aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) activity (males at 1.25 %).

The changes observed at concentrations upwards from 0.4 % (equivalent to a dose of 360 mg/kg bw/day) suggest general systemic toxicity.

In a non-guideline 14-day toxicity study, administration of the chemical via oral gavage at a dose of up to 600 mg/kg bw/day in SD rats (n = 10/dose group, four doses tested) did not produce any treatment-related mortality or clinical signs of toxicity (SCCS, 2010). The only significant chemical-induced changes were abnormal coloured dark yellow or orange urine and yellow and orange staining of the tail and hair coat.

In a non-guideline two-year dietary study in purebred beagle dogs (n = 6/sex), a hair dye formulation (containing the chemical at concentration of 0.28 % along with 14 other hair dye chemicals) produced no significant toxic effects (SCCS, 2010). The maximum dose of the chemical tested was determined to be 0.27 mg/kg bw/day. However, the study is of limited value due to the non-specificity and the low test dose of the chemical.

Dermal

Repeat dose toxicity from dermal exposure cannot be inferred from the limited data available.

In a non-guideline study, a hair dye formulation containing the chemical at 0.5 % produced no signs of systemic toxicity in Eppley Swiss mice (n = 60/sex) when applied topically without occlusion for 20 months (SCCS, 2010). This was a combined toxicity and carcinogenicity study, which tested 14 commercial hair dye formulations in the same study. However, the study is of limited value due to the non-specificity and the low test concentration of the chemical.

Inhalation

No data are available.

Genotoxicity

The chemical is not considered to be genotoxic based on the weight of evidence from the available in vitro and in vivo studies. While in vitro tests for gene mutations and chromosome aberrations produced positive results, all in vivo tests were negative.

The following in vitro data are available (SCCS, 2010):

In a bacterial gene mutation assay (OECD TG 471), the chemical induced biologically relevant and roughly dose-dependent increases in revertant colonies of *Salmonella typhimurium* strains TA98 at the highest dose tested, 5000 µg /plate with metabolic activation. No mutagenic activity was observed in the other tester strains (*S. typhimurium* TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA) with metabolic activation, and with any of the tester strains without metabolic activation. The study concluded that the chemical is mutagenic in bacteria.

In a mouse lymphoma assay (OECD TG 476), cell line L5178Y was exposed to the chemical in an initial assay for four hours (at 25-700 µg/mL) with and without metabolic activation, and for 24 hours in an extended assay (at 1-75 µg/mL) without metabolic

activation. Without metabolic activation, the chemical induced a dose-dependent increase in mutant frequency after four hours; however, in the extended treatment assay (24 hours), only the mid dose (200 µg/mL) and the highest dose (600 µg/mL) elicited a response. With metabolic activation, only one dose (15 µg/mL) produced any effect. The equivocal results were further investigated in two additional assays. The results confirmed that the chemical induced a dose-dependent response both with metabolic activation (after four hours) and without metabolic activation (after four, and 24 hours). The colony size distribution data pointed to an increase in frequency of small colonies, which indicated 'a clastogenic rather than a mutagenic potential' of the chemical (SCCS, 2010).

In a chromosome aberration test (OECD 473), the chemical induced biologically relevant and dose-dependent increases in the number of cells (Chinese hamster ovary (CHO) cells) with chromosome aberrations after four hours of treatment (no significant change was observed at four hours) with the chemical at 500-1000 µg/mL with metabolic activation, and at 180-750 µg/mL without metabolic activation after 20 hours treatment. No effects were reported in the cells after four hours of treatment with the chemical (250-1000 µg/mL) without metabolic activation. The study concluded that the chemical is clastogenic in CHO cells.

The following in vivo data are available (SCCS, 2010):

In a bone marrow micronucleus test (OECD 474), ICR mice were exposed to the chemical in single gavage doses of 0, 250, 500 or 1000 mg/kg bw, for 24 and 48 hours. Biologically relevant increases in micronucleated polychromatic erythrocytes (PCEs) were not observed at any of the test doses. The study concluded that the chemical is not genotoxic in bone marrow cells of mice.

In an unscheduled DNA synthesis (UDS) test (OECD 486), negative results were reported in male SD rats when the chemical was administered via oral gavage at doses 0, 750 or 1500 mg/kg bw. No biologically relevant increases were observed in mean net nuclear grain count or percentage of cells in repair in any of the dosed groups for both two to four hour, and the 12-16 hour treatment times. The study concluded that the chemical is not genotoxic in rats.

In a non-guideline heritable translocation test, a semi-permanent dye containing the chemical at 0.01 % (along with seven other hair dye chemicals) gave negative results in male SD Charles River rats. The male rats (n = 50/dose) were treated with the semi-permanent dye topically twice weekly for 10 weeks and then mated with untreated females. From the resulting litter, two healthy males were picked and raised to maturity and mated with untreated females. No adverse effects were observed in the fertility rates or the average litter sizes, which suggested that frequent topical application of the hair dye caused no stable chromosome rearrangements such as translocations. The study concluded that the hair dye containing the chemical at 0.01 % was not genotoxic in rats.

Carcinogenicity

Carcinogenicity of the chemical cannot be inferred from the limited animal data available. The chemical is a secondary amine and thus prone to nitrosation and formation of carcinogenic N-nitroso-compounds (NOCs) under nitrosating conditions (SCCS, 2012). However, overall mechanistic and structural considerations suggest that compared with other aromatic amines, the chemical has a lower likelihood of being a carcinogen.

In a non-guideline two year dietary study, a hair dye formulation (containing the chemical along with 14 other hair dye chemicals) produced no evidence of carcinogenicity in dogs (beagles, n = 6/sex/dose) (SCCS, 2010). The maximum dose of the chemical tested was determined to be 273 µg/kg bw/ day. However, the study is of limited value due to the non-specificity and the low test dose of the chemical.

In a non-guideline study, a hair dye formulation containing the chemical at 0.5 % produced no unusual tumours in Eppley Swiss mice (n = 60/sex), when applied topically to a shaved interscapular region for 20 months (SCCS, 2010). The chemical was a constituent of one of the 14 commercial formulations tested in this study. Although some of the other formulations contained classified carcinogens, none of them induced tumours indicating low sensitivity of the study. Due to the low sensitivity and non-specificity, the study is of limited value.

Many carcinogens are or can be converted in vivo to reactive electrophilic derivatives, which can interact with DNA to induce a mutational event thereby initiating carcinogenesis (Miller & Miller, 1981; Benigni & Bossa, 2011). Aromatic amines and nitroarenes appear to induce mutations through a biochemical transformation to N-hydroxylamine intermediates, which are activated following phase II conjugation to produce electrophilic nitrenium ions that can covalently bind to DNA (National Institute of Occupational Safety & Health (NIOSH), 1980; Benigni & Bossa, 2011) This is consistent with the positive result given by the chemical in *S. typhimurium* TA98 in the bacterial reverse mutation assay (see **Gentoxicity** section). However, the stability

of the phase II conjugates and the nitrenium ions in vivo depends on the type of substituents and the isomeric position of the nitro group. Studies show that para-substituted nitrobenzene derivatives are more mutagenic compared with ortho- or meta-isomers (Vance & Levin, 1984; Shimizu & Yano, 1986; Assman et al., 1997). The chemical has a nitro group attached in an ortho-position to the amine, which could disrupt the activation of the N-hydroxylamine metabolites. The aliphatic alcohol group in the chemical may also provide a more ready site for metabolism compared with the amine groups and chemically de-stabilise any phase II conjugates or nitrenium ions produced. In mechanistic QSAR analyses, the toxic activity of aromatic amines was demonstrated to correlate with the ease of formation of the N-hydroxylamine and the stability of the nitrenium ion (Benigni et al., 2000). Based on these considerations, the chemical has a lower likelihood of being a carcinogen compared with other aromatic amines.

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does not show specific reproductive or developmental toxicity.

In a developmental toxicity study in SD rats (OECD 414), the chemical at a maximum dose of 500 mg/kg bw/day (administered via oral gavage) produced no effect on body weights, uterine weights of dams, litter observations or cause any gross external, soft tissue or skeletal alterations. The study reported an NOAEL of 500 mg/kg bw/day for maternal and developmental toxicity (SCCS, 2010).

In a non-guideline teratology study, female SD rats (n = 25/dose group) from the sub-chronic feeding study (see **Repeated dose toxicity: Oral** section) were maintained on their initial test diets containing 0, 0.125, 0.4 or 1.25 % of the chemical until mating, then changed to a normal diet during mating. The test diet was resumed at the start of gestation. Females were euthanised after 20 days of gestation and foetuses removed. Although there was a significant decrease in maternal mean body weight gain at 1.25 % (equivalent dose of 1125 mg/kg bw/day), no other significant changes were observed in the average litter size, foetal form or reproduction parameters (CIR, 1994).

In a non-guideline study originally intended to study genotoxicity, male SD rats (n = 20/dose group) from the sub-chronic feeding study (see **Repeated dose toxicity: Oral** section) were taken off their test diets and immediately mated with untreated females. The highest test concentration of the chemical in the study was 1.25 % (equivalent dose of 1125 mg/kg bw/day). Pregnant females were euthanised after 17 days of gestation and foetuses removed. ‘No significant differences were observed in the reproduction parameters between the treated and control groups’ (CIR, 1994).

In a sub-chronic oral toxicity study following OECD TG 408 (see **Repeated dose toxicity: Oral** section), a statistically significant but not dose-related decrease in sperm motility was observed in males at 20 and 50 mg/kg bw/day chemical dose. Despite this observation, there was no evidence of reproductive toxicity following exposure to the chemical (SCCS, 2010).

Several non-guideline reproductive and developmental studies on the effect of hair dye mixtures containing the chemical have reported a NOAEL in rats and rabbits at doses up to 1.55 mg/kg bw/day (SCCS, 2010). However, the studies are of limited value due the non-specificity and the low test doses of the chemical.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are the systemic acute effects (acute toxicity from oral exposure).

Public Risk Characterisation

In Australia, the chemical is reported to be used in permanent and semi-permanent hair dyes.

The EU Cosmetics Regulation restricts the maximum concentration of the chemical in hair dye products to 0.75 % and 1.0 % in oxidative and non-oxidative conditions, respectively. Hair dye formulations in Australia are expected to contain the chemical at similar concentrations. The SCCS is of the opinion that at these concentrations the chemical does not pose a risk to the health

of the consumer (SCCS, 2010). Skin sensitisation is not expected at actual use concentrations. Therefore, the public risk from these chemicals is not considered to be unreasonable.

The chemical is a secondary amine and thus prone to nitrosation and formation of carcinogenic nitrosamines. Hence, the EU Cosmetics Regulation restricts the nitrosamine content to 50 µg/kg (equivalent to 50 ppb); does not allow use with nitrosating agents; and mandates storage in nitrite-free containers. These measures are considered appropriate and should be considered by formulators and importers of hair dyes containing the chemical.

Occupational Risk Characterisation

During product formulation, dermal, oral and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute and potential local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral exposure are implemented. Oral 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.

The data available support hazard classification in HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

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

Formulators and importers of hair dyes containing the chemical should consider measures to minimise potential for nitrosamine formation.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical 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)

[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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral exposure to the chemicals 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 chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

Assman N, Emmrich M, Kampf G and Kaiser M, 1997. Genotoxic activity of important nitrobenzenes and nitroanilines in the Ames test and their structure-activity relationships. Mutat Res. 395(2-3), 139- 144.

Benigni R and Bossa C, 2011. Mechanisms of chemical carcinogenicity and mutagenicity: a review with implications for predictive toxicology. Chem Rev. 111(4), 2507-2536.

Benigni R, Giuliani A, Franke R and Gruska A, 2000. Quantitative structure-activity relationships of mutagenic and carcinogenic aromatic amines. Chem Rev. 100(10), 3697-3714.

Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 2011. Washington DC: Personal Care Products Council.

CosIng. Cosmetic Ingredients and Substances. Accessed June 2017 at http://ec.europa.eu/growth/tools-databases/cosing/

Cosmetic Ingredient Review Expert Panel (CIR, 1994). Final report on the safety assessment of HC Yellow No.2. Accessed May 2017 at http://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr85.pdf

Cosmetic Ingredient Review Expert Panel (CIR, 2011). Final report on the safety assessment of HC Yellow No.2. Accessed May 2017 at http://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR609.pdf

European Chemicals Agency (ECHA). Classification and Labelling (C&L) Inventory. Accessed May 2017 at http://echa.europa.eu/information-on-chemicals/cl-inventory

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.).

European Union Cosmetics Regulation (EC) No 1223/2009 Annex III of the European Parliament and of the council. Accessed at http://ec.europa.eu/growth/tools-databases/cosing/

Galleria Chemica. Accessed May 2017 at http://jr.chemwatch.net/galleria/

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

Miller E and Miller J, 1981. Searches for ultimate chemical carcinogens and their reactions with cellular macromolecules. Cancer. 47(10), 2327-45.

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

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

NIOSH (1980). The carcinogenicity and metabolism of azo dyes, especially those derived from benzidine. National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services publication volumes 80-119.

OECD (2004), SIDS initial assessment report for 2-nitroaniline (88-74-4). Accessed May 2017 at http://webnet.oecd.org/HPV/UI/Search.aspx

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

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

Scientific Committee on Consumer Safety (SCCS) 2010. Opinion on HC Yellow n° 2, COLIPA N° B41. SCCS/1309/10. Adopted at the 8th plenary meeting of 21st September 2010. Available at https://ec.europa.eu/health/scientific_committees/consumer_safety/.../sccs_o_038.pdf

Scientific Committee on Consumer Safety (SCCS) 2012. Opinion on nitrosamines and secondary amines in cosmetic products. Adopted at its 14th plenary meeting of 27 March 2012. Accessed June 2017 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_090.pdf

Shimizu M and Yano E, 1986. Mutagenicity of mono-nitrobenzene derivatives in the Ames test and rec assay, Mutat Res. 170(1-2), 11-22.

The Poisons Standard, June 2017. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 17. Accessed at https://www.tga.gov.au/publication/poisons-standard-susmp

United States (US) Department of Health and Human Services Household Product Database. Accessed May 2017 at https://householdproducts.nlm.nih.gov/about.htm

Vance WA and Levin DE, 1984. Structural features of nitroaromatics that determine mutagenic activity in Salmonella typhimurium. Environ Mutagen. 6(6), 797-811.

Last update 30 June 2017