Ethanol, 2-[(2-amino-4-nitrophenyl)amino]-: Human health tier II assessment

27 October 2017

CAS Number: 56932-44-6

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.

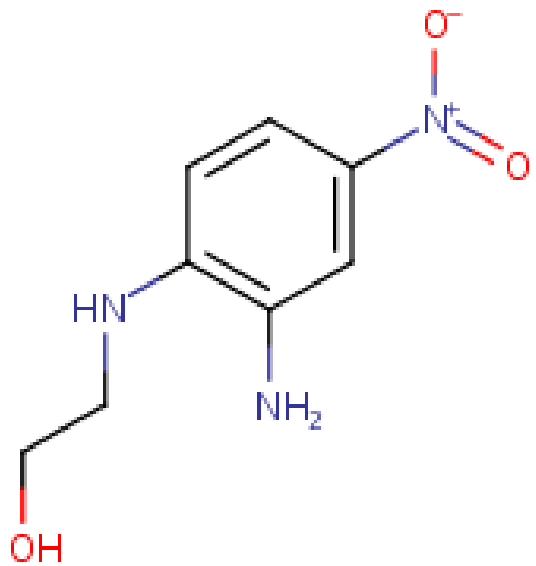
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	HC Yellow No. 5 N1-(2-hydroxyethyl)-4-nitro-o-phenylenediamine
Structural Formula	
Molecular Formula	C8H11N3O3
Molecular Weight (g/mol)	197.20
SMILES	c1(NCCO)c(N)cc(N(=O)=O)cc1

Import, Manufacture and Use

Australian

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

The chemical has reported cosmetic use in permanent and semi-permanent dye preparations.

International

The following international uses have been identified through Galleria Chemica; the European Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the Cosmetic Ingredient Review Report (CIR, 2004) and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use as a hair dye ingredient in non-oxidative, semi-permanent hair dye products. The chemical is also used as a toner in permanent, oxidative hair dyes. The US Food and Drug Administration (FDA) reported that the chemical is used in 37 products such as hair dye and colour, and hair tints. The chemical is currently used at 1.6 % in hair dyes and 0.2 % in hair tints (CIR, 2004).

Restrictions

Australian

The chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 6 and 10 (SUSMP, 2017).

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 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 6 chemicals are described as '**Poison** - Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'(SUSMP, 2017).

Schedule 10 chemicals are described as '**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, 2017).

International

The chemical is listed on the European Union (EU) Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products (CosIng; Galleria Chemica). It is also listed on the European Commission (EC) List of 181 substances banned for use in hair dye products (EC, 2015).

It is listed on the Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1—List of substances which must not form part of the composition of cosmetic products (Galleria Chemica).

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

The dermal absorption of this chemical in hair dye formulations was investigated in Sprague Dawley (SD) rats and low percutaneous absorption was seen.

In a percutaneous penetration study, radiolabelled chemical (^{14}C-labelled) in aqueous solution was applied to a clipped (3 cm^2) dorsal skin on Sprague Dawley (SD) rats (n=6/group) for 30 minutes at doses of 0.2 mL chemical solution (mean dose of 31.4 mg/kg), and 0.1 mL chemical solution and 0.1 mL hydrogen peroxide developer (mean dose of 15.1 mg/kg). The test materials were subsequently removed with spatula, followed by shampooing and rinsing. The overall skin penetration was 0.054 % with the hair dye alone and 0.124 % with the hair dye and developer. The majority of the applied dose was found in post-treatment

rinse water. A very small amount of the chemical was absorbed and excreted via urine (approximately 70 % of the absorbed dose) within the first 24 hours. (CIR, 2004).

Acute Toxicity

Oral

The chemical has moderate acute toxicity based on the results from the animal tests, warranting hazard classification (see **Recommendation** section).

Rats (n=2/sex/dose) were administered the chemical (10 % suspension in water) as a single dose of 0, 250, 500, 625 or 750 mg/kg bw by gavage. All animals survived at 250 mg/kg bw. One female died at 500 mg/kg bw; three animals died at 625 mg/kg bw; and all animals died at 750 mg/kg bw. The calculated mean lethal dose (LD50) for both sexes was 555.56 mg/kg bw (CIR, 2004).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is only slightly irritating to skin.

In a skin irritation study, six New Zealand White (NZW) rabbits were topically administered the chemical (0.1 % in water) on shaved skin and on shaved/abraded skin. Observations were recorded at 24 and 72 hours after application. Mild erythema in two rabbits was reported after 24 hours, which resolved within 72 hours. The average irritation indices were reported to be 0.08 and 0.04 for shaved animals and shaved/abraded animals, respectively. A total primary irritation index (combined) of 0.12 was reported (CIR, 2004).

Eye Irritation

The chemical is not an eye irritant.

In an eye irritation study, 0.1 mL of the chemical (0.1 % in water) was instilled in the left conjunctival sac of nine albino rabbits. The test material was left in the eye for 4 seconds before rinsing (3 animals), 30 seconds before rinsing (3 animals) or without rinsing (3 animals). The right eye served as a control. Animals were observed for seven days after treatment. No signs of eye irritation were reported (CIR, 2004).

Sensitisation

Skin Sensitisation

The chemical is not a skin sensitiser based on the negative results obtained from a guinea pig maximisation test (GMPT).

In a maximisation test, guinea pigs (n=20/sex/group) were intradermally injected (induction) with Freund's complete adjuvant (FCA) diluted 1:1 in water; 1 % of the chemical or the positive control (0.005 % 1-choloro-2,4-dinitrobenzol; DNCB). On the next day, sodium lauryl sulfate (10 % in petrolatum) was dermally applied with abrasion. Six to eight hours later, all animals were dermally applied (topical induction) 1 % chemical, 0.025 % DNCB and water (negative control) in petrolatum. A challenge dose comprising of decreasing concentrations of the chemical (1, 0.5 and 0.25 % in water) was topically applied 14 days post induction. Observations were made at 48 hours. No signs of local irritation or sensitisation were observed (CIR, 2004).

Repeated Dose Toxicity

Oral

Based on the limited available data, the chemical is not expected to be harmful to health following repeated oral exposure.

In a 24-month chronic study, groups of beagle dogs (n=6/sex/dose) were fed the chemical in their diet at 0, 19.5 or 97.5 mg/kg bw/day. Necropsy was conducted (1 animal/sex/dose) at 6, 12 and 18 months. All survivors were necropsied at 24 months. Blue/black coloured urine was reported. No mortalities or signs of toxicity were observed (CIR, 2004).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

In vitro studies

In a bacterial gene mutation assay, the chemical gave positive results in *Salmonella typhimurium* strains TA98, TA100 and TA 1537 treated at 8, 40, 200, 1000 and 5000 µg/plate, with and without metabolic activation. No increase in the number of revertants was seen in strain TA1535 at any concentration tested (CIR, 2004).

In a mouse lymphoma assay, the chemical was tested on mouse lymphoma L5178Y cells at concentrations of 0.46, 1.37, 4.11, 12.3, 37.0, 111.1, 333.3 or 1000 µg/mL, with and without metabolic activation. No significant increase in the resistant cells with or without metabolic activation was reported (CIR, 2004). In another in vitro mammalian cell gene mutation assay, the chemical did not induce mutation in Chinese hamster V79 cells at doses up to 2000 µg/mL with or without metabolic activation.

In a chromosomal aberration test conducted in human peripheral blood lymphocytes, the chemical did not induce significant increases in the number of aberrations with and without metabolic activation at concentrations of 30, 100 and 300 µg/mL (CIR, 2004).

In a Chinese hamster ovary cells assay, the chemical did not induce increases in chromosomal aberrations with or without activation at concentrations up to 1500 µg/mL (CIR, 2004).

In vivo studies

The available in vivo studies gave negative results (CIR, 2004).

In two independent mice micronucleus tests, the chemical dissolved in dimethylsulfoxide (DMSO) was administered as a single dose in three groups of mice (5/sex/group) at 150 (Crl:NMRI BR mice by intubation) or 240 mg/kg bw (CFLP mice by intraperitoneal injections). The animals were euthanised at 24, 48 and 72 hours after administration. No increases in micronucleated polychromatic erythrocytes in bone marrow samples were reported (CIR, 2004).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a fertility study, groups of SD rats (n=60 males; 120 females) were administered the chemical at 0, 1950 or 7800 ppm in their diet, eight weeks prior to mating, during mating and until 21 days of lactation. No significant changes in fertility in both sexes; length of gestation; number of live and resorbed foetuses per litter; pup body weights; or pup survival were observed (CIR, 2004).

Female NZW rabbits (n=48/dose) were administered the chemical at 19.5 or 97.5 mg/kg bw/day on gestation days (GD) 6–18. Blue-brown discolouration of urine was seen in animals at 97.5 mg/kg bw/day. No changes in the foetal survival rate, gross abnormalities, or soft tissue defects were reported. Although some variations in the degree of ossification and in the number of ribs were reported, these changes were not considered to be treatment-related (CIR, 2004).

In a teratology study, female SD rats (n=10-13/dose) were orally administered the chemical at doses of 50, 100 or 200 mg/kg bw/day on GD 6–15. Significant decrease in the mean maternal weight gains were reported on GD 6–15 in the 200 mg/kg bw/day group. However, a significant increase in mean maternal weight gain was reported in the same dose group during post-treatment period of days 16–20. No teratogenic effects were reported (CIR, 2004).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is systemic 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 chemical is listed on the European Union (EU) Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products (CosIng; Galleria Chemica) and the European Commission (EC) List of 181 substances banned for use in hair dye products (EC, 2015).

In Australia, the chemical is controlled as part of the 'PHENYLENEDIAMINES' chemical group. Phenylenediamines (including alkylated, arylated and nitro derivatives) are listed on Schedules 6 and 10 of the SUSMP with restrictions and prohibitions on their use in specific cosmetic products (including hair dyes). Warning statements, first aid instructions and safety directions apply to chemicals covered by the Schedule 6 group entry. Schedule 10 group entry prohibits the sale, supply and use of the chemical in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows **except** when included in Schedule 6. The current controls are considered adequate to minimise the risk of acute toxicity to the public posed by hair dyes containing the chemical.

Occupational Risk Characterisation

During product formulation, oral and dermal 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 health effect, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral and dermal exposure are implemented. 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 a new hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

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

Regulatory Control

Public Health

The chemical falls within the scope of the listing of ‘Phenylenediamines’ in Schedule 6 and 10 of the SUSMP for use in hair dye preparations under specific conditions. No additional controls are required.

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)

[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;
- 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

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2007. List of Chemicals used as Dyes in Permanent and Semi-Permanent Hair Dyes in Australia.

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

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2017, No. 18. Accessed October 2017 at https://www.legislation.gov.au/Details/F2017L01285

The US Environmental Protection Agency (EPA) Aggregated Computer Toxicology Resource (ACToR) database. Accessed July 2017 at https://actor.epa.gov

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