1,2-Ethanediamine, N-(5-methoxy-2-nitrophenyl)-, monohydrochloride: Human health tier II assessment

29 June 2018

CAS Number: 86419-69-4

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.

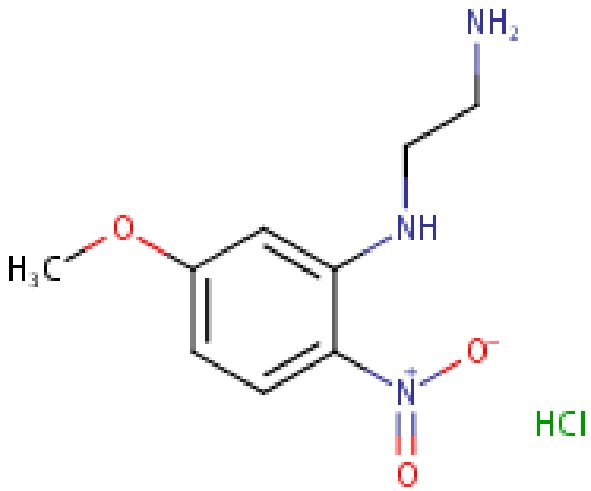
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	ethylenediamine, N-(5-methoxy-2-nitrophenyl)-, hydrochloride HC Yellow no. 9 Imexine FAD N-(5-methoxy-2-nitrophenyl)-1,2-ethanediaminemonohydrochloride
Structural Formula	
Molecular Formula	C9H13N3O3.ClH
Molecular Weight (g/mol)	247.68
Appearance and Odour (where available)	yellow crystalline powder, almost odourless
SMILES	c1(N(=O)=O)c(NCCN)cc(OC)cc1_Cl

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 in non-oxidative (semi-permanent) hair dye products at a maximum concentration of 0.5 % in the EU (SCCS, 2010) and as a hair colourant in the US (Personal Care Products Council).

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Council Directive 2012/21/EU — No. 658/2013 Annex III/259; and
- ASEAN Cosmetic Directive Annex III.

The restrictions in the EU and ASEAN include:

- maximum concentration in finished cosmetic products is 0.5 % (calculated as hydrochloride);
- do not use with nitrosating agents;
- maximum nitrosamine content of 50 µg/kg; and
- keep in nitrite-free containers.

The ASEAN Directive has the following additional restrictions:

- use for dyeing eyelashes and eyebrows is not permitted; and
- the direction for use “wear suitable gloves” must be included in label or leaflet text.

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

Available data show that up to 9 % of the chemical is absorbed through human skin when used in hair dyes. An additional portion of the chemical (up to 14 %) appears to remain bound to the outermost layer of the skin. Due to the constant shedding of the outermost layer of skin cells, this portion of the chemical may not be bioavailable for further absorption (Wolfram & Maibach, 1985).

In a guideline study (OECD Test Guideline (TG) 428), in vitro dermal absorption of the chemical (0.41 % in a 'commercial type' formulation) was determined in human dermatomed skin (SCCS, 2010). The chemical distribution (as % of the applied dose) analysed 24 hours following a 30 minute exposure period were as follows:

- receptor fluid—0.19 ± 0.21 % (0.15 ± 0.17 µg/cm^2);
- stratum corneum—7.56 ± 6.12 % (6.05 ± 4.90 µg/cm^2);
- epidermis and dermis—5.70 ± 2.94 % (4.54 ± 2.32 µg/cm^2); and
- total absorption (receptor fluid + epidermis + dermis)—5.89 ± 3.05 % (4.69 ± 2.41 µg/cm^2).

After correcting for the intended use concentration, a value of 9.51 µg/ cm^2 (mean + 2 standard deviation) was determined for calculation of margin of safety (SCCS, 2010) (see **Public risk characterisation** section).

A study in rats showed that the chemical was readily absorbed following oral exposure (SCCS, 2010).

Acute Toxicity

Oral

Based on data from a guideline study, the chemical has moderate acute toxicity following oral exposure with median lethal dose (LD50) value in the range of 200–500 mg/kg bw in rats, warranting hazard classification (see **Recommendation** section).

A guideline acute oral toxicity study (OEDC TG 420) reported an LD50 between 200–500 mg/kg bw in Sprague Dawley (SD) rats (SCCS, 2010). Adverse effects observed prior to death included piloerection, decreased activity and/or rigidity of body

accompanied by uncontrolled seizures (tonic clonic convulsions). No clinical or pathological signs were observed in the surviving rats.

A non-guideline study in SD rats (n = 5/sex/dose) reported an LD50 of 745 mg/kg bw in males and 1609 mg/kg bw in females (SCCNFP, 2003; SCCS, 2010). The test doses delivered by oral gavage ranged from 700–2000 mg/kg bw in both sexes. Due to the absence of information on the purity of the test substance, this study is only of supportive value.

Dermal

No data are available. Whilst the chemical has moderate acute toxicity following oral exposure, it is expected to have comparatively low dermal absorption from hair dyes (see **Toxicokinetics** section).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on available data, the chemical is not irritating to skin.

In an acute dermal irritation study in rabbits (OECD TG 404) (SCCS, 2010), the chemical at 5 % did not cause oedema (swelling). The chemical stained the skin yellow at the application sites, which prevented accurate evaluation and scoring of erythema (redness). Although staining of the skin may have masked possible erythema, due to the absence of any other skin reactions, the chemical is not considered to be irritating to rabbit skin .

A non-guideline study in New Zealand albino rabbits (n = 3) reported a primary irritation score of 0.3, classifying the chemical as a non-irritant (SCCNF, 2003; SCCS, 2010). An occlusive patch containing the neat chemical moistened with distilled water was dermally applied for 24 hours. Although yellow staining was seen on the application sites, it was reported not to interfere with evaluation of erythema. Erythema was reported in 2 of 3 animals, 1 hour after treatment on both intact and abraded application sites but not at 48 hours. No other skin reactions were seen.

Eye Irritation

Based on available data, the chemical is slightly irritating to eyes. However, the reported scores do not support hazard classification.

In an acute eye irritation study in rabbits (OECD TG 405), the chemical at 5 % produced very slight conjunctival redness (average score of 0.3) and very slight chemosis (swelling) (average score of 0.3) in 1 of 3 animals observed over 72 hours (3 days) (SCCS, 2010). The effects were fully reversed by day 4 in all animals. No corneal opacity or iris lesions were reported.

In a non-guideline eye irritation study in New Zealand albino rabbits (n = 3), the chemical applied as a neat substance to eye lids and left unrinsed, produced the following effects (SCCNF, 2003; SCCS, 2010):

- irritation of the conjunctiva in all animals;
- dulling of the cornea in 1 animal; and
- inflammation and yellow staining of the iris in 1 animal.

The effects were fully reversed by day 3 in all animals. The study reported a maximum irritancy score of 17.7/110, which indicates the chemical is slightly irritating to eyes.

Sensitisation

Skin Sensitisation

Based on local lymph node assay (LLNA) data, the chemical is not expected to induce skin sensitisation at concentrations up to 1 %.

In an LLNA study (OECD TG 429), the chemical at concentrations up to 1 % in dimethyl sulfoxide (DMSO) did not induce sensitisation in mice (SCCS, 2010). The threshold threefold increase in lymphocyte proliferation (EC3) was not reached at any of the test concentrations as indicated by the stimulation indexes (SI)—1.15 (0.5 %), 1.20 (0.1 %), 1.12 (0.25 %), 1.73 (0.5 %) and 1.12 (1 %). However, sensitising potential of the chemical cannot be excluded since the chemical was tested at low concentrations (SCCS, 2010).

In a non-guideline study, dermal response to the chemical was assessed in Dunkin-Hartley guinea pigs (n = 10/sex) for up to 24 hours after the following treatment (SCCNF, 2003; SCCS, 2010):

- intradermal injection with 50 % Freund's complete adjuvant (FCA) followed by topical induction with the chemical (neat substance) applied as a 48-hour patch (total of 7 applications from days 1–15); and
- topical challenge with the chemical (neat substance) applied as a single 48-hour occlusive patch.

Staining of the skin caused by the chemical at application sites prevented evaluation of erythema (redness). No oedema (swelling) or other skin reactions were observed.

Repeated Dose Toxicity

Oral

Based on available data, the chemical is not expected to cause serious damage to health on repeated oral exposure.

In a 90-day oral toxicity study (OECD TG 408), a no observed adverse effect level (NOAEL) of 250 mg/kg bw/day was determined for the chemical (dosed at 0, 25, 80 and 250 mg/kg bw/day) in rats (SCCS, 2010). The only treatment-related adverse effect was a dose-related increase in hypersalivation. All other histopathological and biochemical changes were within the historical control range.

Dermal

No data are available. Considering the low toxicity on repeated oral exposure and low dermal absorption, the chemical is not expected to cause serious damage to health on repeated dermal exposure.

Inhalation

No data are available.

Genotoxicity

The chemical is not considered to be genotoxic based on weight of evidence from available data. While the chemical was positive in one of the in vitro studies, the positive results were not confirmed in an equivalent study in vivo.

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

The chemical was not mutagenic in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA (at 62–1000 µg/plate), with and without metabolic activation.

The chemical was genotoxic in a chromosomal aberration test (OECD TG 473) in Chinese hamster ovary (CHO) cells. The chemical induced biologically relevant increases in percentage of cells with chromosomal aberrations at both 24 and 48 hours after treatment with the chemical at 50–500 µg/mL without metabolic activation. No increases were seen in the presence of metabolic activation.

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

The chemical was not genotoxic in an in vivo mammalian erythrocyte micronucleus test (OECD TG 474). The chemical did not induce an increase in micronucleated polychromatic erythrocytes (indicating a non-interference with chromosomal structure and distribution) in the bone marrow cells of mice dosed up to 100 mg/kg bw/day.

The chemical was not genotoxic in an in vivo unscheduled DNA synthesis (UDS) test (OECD TG 486) in rats. The chemical did not induced UDS in liver cells (hepatocytes) of rats dosed up to 750 mg/kg bw/day.

Carcinogenicity

No data are 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).

Reproductive and Developmental Toxicity

Based on available data, the chemical is not expected to cause specific developmental toxicity. No data are available for reproductive toxicity.

In a prenatal development toxicity study (OECD TG 414), a maternal NOAEL of 70 mg/kg/day was determined for the chemical in female rats dosed at 0, 20, 70 or 250 mg/kg bw/day on days 6–15 after mating (SCCNFP, 2003; SCCS, 2010). There were no animal deaths. One animal in the highest dose group displayed piloerection, round back and emaciation on the last day of gestation (day 20). Other treatment-related adverse effects in the pregnant females included reduced body weight and food consumption in the highest dose group, and yellow coloured urine in animals dosed at 70 and 250 mg/kg bw. No treatment-related effects were observed on foetal development. The chemical produced maternal toxicity at 250 mg/kg bw but was not embryotoxic or teratogenic at any of the doses tested.

Risk Characterisation

Critical Health Effects

The available data are limited on relevant critical health end points such as skin sensitisation and carcinogenicity. The chemical was not a skin sensitiser up to a concentration of 1 %.

The chemical can cause harmful effects following single oral exposure.

Public Risk Characterisation

The chemical is reported to be used in hair dyes in Australia (NICNAS, 2007). Currently, there are no restrictions on using the chemical in cosmetic products in Australia.

The ASEAN and the EU have restricted the use of the chemical in non-oxidative hair dyes to a maximum concentration of 0.5 % in finished cosmetic products (see **Restrictions: International** section). Hair dye products in Australia are expected to contain the chemical at similar concentrations. Following a safety evaluation, the Scientific Committee on Consumer Safety (SCCS) concluded

that the use of the chemical as a non-oxidative hair dye ingredient at a maximum on-head concentration of 0.5 % does not pose a risk to the health of the consumer, apart from possible sensitising potential (SCCS, 2010).

A margin of safety (MOS) of 761 was calculated for the chemical using dermal absorption value of 9.51 µg/ cm^2 (see **Toxicokinetics** section) and a NOAEL of 70 mg/kg/day from developmental study (see **Reproductive and developmental toxicity** section). A cosmetic ingredient with a MOS of at least 100 is generally considered safe for use (SCCS, 2016).

As a substituted phenylenediamine, the chemical belongs to a class of known skin sensitisers. However, the chemical is not expected to induce skin sensitisation at the actual use concentrations. Overall, the public risk from the chemical in cosmetics is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal and ocular exposure might 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. Good hygiene practices to minimise oral exposure are expected to be in place.

Given the critical health effect (and limited data on availability on some health endpoints), the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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 hazard classification of the chemical (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.

Regulatory Control

Public Health

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	Toxic if swallowed - Cat. 3 (H301)

[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 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;
- 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.

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Last update 29 June 2018

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