Phenol, 2-[(2-hydroxyethyl)amino]-5-nitro-: Human health tier II assessment

01 September 2015

CAS Number: 73388-54-2

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

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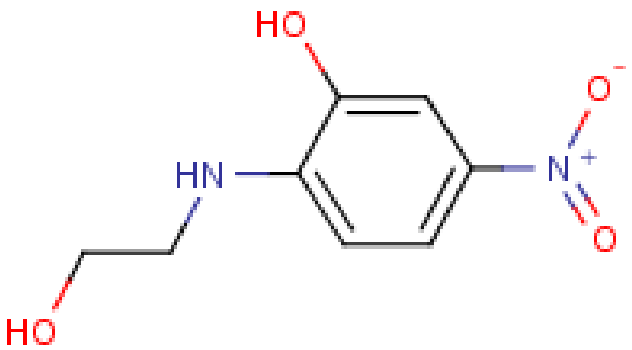
Acronyms & Abbreviations

Chemical Identity

Synonyms	HC Yellow no. 11 2-((2-hydroxyethyl)amino)-5-nitrophenol 3-nitro-6-N-beta-hydroxyethylaminophenol Imexine FW
Structural Formula	
Molecular Formula	C8H10N2O4
Molecular Weight (g/mol)	198.177
Appearance and Odour (where available)	Brownish crystalline powder, almost odourless
SMILES	c1(NCCO)c(O)cc(N(=O)=O)cc1

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).

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

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development (OECD) Screening Information Dataset Initial Assessment Report (SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), the US National Library of Medicine's Hazardous Substances Data Bank (HSDB) and various international assessments including from the Scientific Committee on Consumer Safety (SCCS) and Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP).

The chemical has reported cosmetic use in semi-permanent hair dye formulations.

The maximum concentration in semi-permanent hair dyes was reported to be 1.1 % (SCCNFP, 2003).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II - Part 1: List of substances which must not form part of the composition of cosmetic products;
- EC Cosmetics Regulation No. 1223/2009 Annex II - List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components cosmetic products must not contain.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The chemical is a secondary alkanolamine and has a potential for nitrosation that could lead to carcinogenicity (SCCNFP, 2003; SCCS, 2011).

Toxicokinetics

The chemical was reported to have very little absorption through the human dermatomed skin samples (0.13 ± 0.07 µg/cm^2) in an in vitro percutaneous absorption study conducted using the COLIPA guidelines (SCCNFP, 2003).

Acute Toxicity

Oral

The chemical has a low acute oral toxicity in rats.

The median lethal dose (LD50) in Sprague Dawley (SD) rats was reported to be greater than 5000 mg/kg bw in a study conducted according to the OECD Test Guideline (TG) 401 (SCCNFP, 2003).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is not a skin irritant.

The chemical (0.5 g moistened with water) as occlusive patches was applied to the skin of three New Zealand White rabbits for 24 hours (Journal Officiel de la Republique Francaise, 21/02/82 test guidelines). Only slight erythema and staining of the skin were observed at one, 24 and 72 hours after removal of the patches. The mean primary irritation index was 0.5/8. The chemical was reported to be not irritating to the skin (SCCNFP, 2003).

Eye Irritation

The chemical is a slight eye irritant, not warranting hazard classification.

The chemical (0.1 mL or 0.057 g) was applied to the right eye of three New Zealand White rabbits without rinsing (Journal Officiel de la Republique Francaise, 24/10/84 test guidelines). Observations were made at one hour and 1, 2, 3, 4 and 7 days after application. All three rabbits showed irritated conjunctivae, including one which also had the cornea and iris affected by the treatment, that resolved within three days. The mean ocular irritation index according to Draize was calculated to be 7 out of a maximum of 110, indicating the chemical as a slight eye irritant (SCCNFP, 2003).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical may be a weak skin sensitiser, but does not meet the criteria for the method for hazard classification.

In a Magnusson and Kligman skin sensitisation test (OECD TG 406), female Dunkin-Hartley guinea pigs were induced using two pairs of three intradermal injections of 50 % Freund’s complete adjuvant (FCA), the chemical at 5 % (in arachis oil) and a mixture of both. Six days later, 10 % sodium lauryl sulphate (0.5 mL) was applied at injection sites and on the seventh day, the animals were challenged applying the chemical at 75 % (in arachis oil) as an occlusive patch (0.5 mL) for 48 hours. Skin examinations at 24 and 48 hours after challenge showed only 1/20 animals having a positive reaction. The chemical was reported as a weak skin sensitiser (SCCNFP, 2003).

Repeated Dose Toxicity

Oral

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

In a 13-week oral gavage study (OECD TG 408), SD rats (n=10 per sex/dose) were administered the chemical at doses of 0, 50, 200 or 800 mg/kg bw/day. Two females died at 800 mg/kg bw/day (on day 22 and 63). Treated males showed a dose-related decrease in creatinine levels (significant at 200 and 800 mg/kg bw/day, compared with the control group). A no observed adverse effect level (NOAEL) of 50 mg/kg bw/day was established based on effects observed at higher concentrations (significantly increased liver and kidney weights, significantly decreased thymus weight and centrilobular hepatocyte hypertrophy) (SCCNFP, 2003).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the negative in vivo genotoxicity data, the chemical is not expected to have mutagenic potential.

All three in vitro genotoxicity assays available for the chemical showed some positive results under certain test conditions (SCCNFP, 2003):

- A bacterial reverse mutation assay (OECD TG 471) used *Escherichia coli* strain WP2uvrA and *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at 156.25-5000 µg/plate, with or without metabolic activation. Only *S. typhimurium* strain TA98 showed positive results with metabolic activation.
- In a gene mutation test (OECD TG 476), L5178Y mouse lymphoma cells were exposed to the chemical at 125-1000 µg/mL for two hours, with or without metabolic activation. A significant increase in mutant frequency (increased by a factor of 3.5 compared with controls) was observed only at 1000 µg/mL, with metabolic activation. However, a strong precipitate occurred at 1000 µg/mL under the basic pH (8 - 8.5) test conditions.
- In a mammalian chromosome aberration test (OECD TG 473), human blood lymphocytes were exposed to the chemical at 250-800 µg/mL for 3, 20 or 44 hours, with or without metabolic activation. Significant increases in chromosome aberrations were reported at 750 µg/mL incubated for three hours, with or without metabolic activation, and at 800 µg/mL incubated for 20 hours, only with metabolic activation.

Two in vivo genotoxicity studies showed negative results for the chemical (SCCNFP, 2003):

- In a micronucleus test (OECD TG 474), OF1 mice (n=5 per sex/dose) were administered the chemical by oral gavage at 0, 500, 1000 or 2000 mg/kg bw/day for two days. There was no significant increase in the incidence of micronucleated polychromatic bone marrow cells.
- In an unscheduled DNA synthesis (UDS) test (draft OECD TG of 1991), four male Wistar rats were administered a single gavage dose of the chemical at 0, 200 or 2000 mg/kg bw. No increased unscheduled DNA synthesis was observed in hepatocytes isolated at 2 or 16 hours after treatment.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemical. The chemical structure and reaction mechanisms for carcinogenicity suggest that the chemical may have some carcinogenic potential. However, the information available is insufficient to warrant hazard classification.

The chemical was reported to produce carcinogenic nitrosamine (SCCNFP, 2003; SCCS, 2012). Secondary aromatic amines are in general among the most reactive amines towards nitrosating agents, generating nitrosamines (SCCS, 2011). They undergo metabolic activation, usually involving N-hydroxylation and eventual formation of highly reactive nitrenium ions. The nitrenium ions bind covalently to biomolecules such as DNA, generating DNA adducts (Benigni and Bossa, 2011).

The generation of electrophilic nitrenium ions can also arise from the metabolic activation of the nitro-group. The stability of the nitrenium ion is correlated with mutagenicity, and depends on the type of substituents and isomeric position of the nitro group. The *p*-substituted nitrobenzene derivatives possess higher mutagenicity, compared to *o*- or *m*-isomers (Vance et al., 1984; Shimizu et al., 1986; Lee et al., 2005). The chemical has shown positive results only in some in vitro genotoxicity assays (see **Genotoxicity**). Importantly, it gave a positive result in *S. typhimurium* TA98 in the presence of metabolic activation, which is consistent with carcinogenic activity with a nitrenium ion mechanism (Benigni and Bossa, 2011).

For the chemical, which presents both amino and nitro groups, a higher reactivity of the aromatic amino group with respect to the aromatic nitro group is expected. Also, it was reported that 'the carcinogenicity of nitro-compounds containing aromatic amines increases with the aromaticity of the aromatic ring attached to the amine group' (Benigni and Bossa, 2011).

Reproductive and Developmental Toxicity

Based on the available information, the chemical is not considered to have specific reproductive or developmental toxicity.

Twenty five female SD rats were administered the chemical by oral gavage at doses of 0, 20, 200 or 2000 mg/kg bw/day during gestation day (GD) 6-15 and sacrificed on GD 20 (OECD TG 414). No treatment-related developmental effects were observed at any dose. The control group and the treated groups had similar mean numbers of corpora lutea, implantation sites, post-implantation loss and live foetuses with similar body weights. The NOAEL for maternal toxicity was reported to be 200 mg/kg bw/day, based on decreased food consumption and body weight gain at the highest dose (SCCNFP, 2003).

Risk Characterisation

Critical Health Effects

Based on the available toxicity data, the chemical may cause only slight eye irritation and weak skin sensitisation. Therefore, the chemical is not classified as a hazardous substance. However, data on acute or repeated dose dermal and inhalation toxicity, and carcinogenicity are not available.

The chemical structure and reaction mechanisms indicate that carcinogenic potential of the chemical cannot be ruled out. As the chemical is a secondary alkanolamine, it has the potential for nitrosation. However, the nitrosamine content of the chemical can vary depending on the batches of the chemical produced. The SCCNFP report (2003) stated that the information available on the chemical is inadequate to assess the safe use of the chemical.

Public Risk Characterisation

The chemical was reported to be used in semi-permanent hair dyes in Australia in 2007. The maximum concentration of the chemical in semi-permanent hair dyes was reported to be 1.1% (SCCNFP, 2003). Many countries in the European Union and New Zealand have prohibited the use of this chemical in cosmetics, for which the decision may be based on its potential for nitrosation. Currently, there are no restrictions on using this chemical in Australia.

If this chemical is included in products containing N-nitrosating agents, carcinogenic nitrosamine compounds could be formed (SCCS, 2012).

Considering the use in hair dyes, the main route of public exposure to the chemical is expected to be through the skin. If the chemical has potential for carcinogenicity, it may pose an unreasonable risk under the identified use.

Occupational Risk Characterisation

During product formulation, exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may 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.

The data available are not conclusive to classify the chemical as a hazardous substance.

NICNAS Recommendation

The chemical was reported to be used in semi-permanent hair dyes in Australia in 2007. However, there are international restrictions on using this chemical in cosmetics (including in hair dyes). Also, hazard data for important health end points of the chemical are lacking or inconclusive.

The chemical is recommended for a Tier III assessment to determine whether it is still used in semi-permanent hair dyes in Australia. If the chemical is used in hair dyes in Australia, further regulatory controls may be required to manage the potential risks.

Regulatory Control

Public Health

The need for regulatory control for public health will be determined as part of the Tier III assessment.

Work Health and Safety

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory.

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 chemicals has not been undertaken as part of this assessment.

References

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Last update 01 September 2015

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