Ethanol, 2-[3-(methylamino)-4-nitrophenoxy]-: Human health tier II assessment

27 November 2014

CAS Number: 59820-63-2

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.

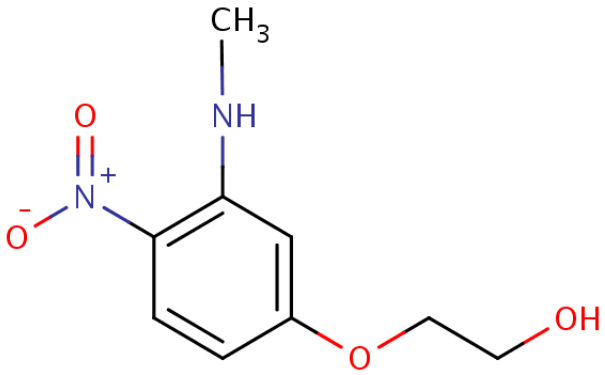
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	3-methylamino-4-nitro-phenoxyethanol 4-?nitro-?3-?methylaminophenoxyet?hanol ethanol,2-(3-methylamino)-4-nitrophenoxy)-
Structural Formula	
Molecular Formula	C9H12N2O4
Molecular Weight (g/mol)	212.20
Appearance and Odour (where available)	Odourless, yellow crystalline powder.
SMILES	c1(N(=O)=O)c(NC)cc(OCCO)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 Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetics Ingredients (INCI) Dictionary; and eChemPortal: the US Environmental Protection Agency (EPA) Aggregated Computer Toxicology Resource (ACToR).

The chemical has reported cosmetic use in non-oxidative hair dye preparations.

The chemical is reported to be safe for use in hair dyes at concentrations up to a maximum of 0.15 % (US Cosmetic Ingredient Review (CIR, 2008).

Restrictions

Australian

No known restrictions have been identified.

International

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

- European Union (EU) Cosmetics Regulation 1223/2009 Annex III: List of substances which cosmetic products must not contain except subject to the restrictions laid down—in non-oxidative hair dye products at 0.15 % as the maximum concentration in ready for use preparations;
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down; and
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.

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

Toxicokinetics

In a percutaneous absorption assay (conducted according to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 428), eight skin membrane samples were treated with ^{14}C radiolabelled chemical at a 0.15 % concentration. Perfusion samples were collected at 1, 2, 3, 4 hours and then 2 hourly intervals up to 24 hours post exposure. The mean recovery of the chemical was 95.2 % in a final wash of the sample skin with a maximum skin absorption of 0.19 $\mu g/cm^2$ (CIR, 2008).

Acute Toxicity

Oral

The chemical has moderate acute toxicity in animal tests following oral exposure, warranting a hazard classification.

The median lethal dose (LD50) in female Sprague Dawley (SD) rats is 1000–2000 mg/kg bw (CIR, 2008). Observed sublethal effects included lethargy, increasing weakness, goosebumps and shortness of breath.

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Only limited data are available. The chemical was not a skin irritant in rabbits at 2 % concentration.

A group of male New Zealand White rabbits (n = 3) was treated with a 2 % solution of the chemical on the shaved intact skin (semi-occlusive patch) for four hours (OECD TG 404). There was no sign of irritation at 1, 24, 48 and 72 hours after the removal of the patch (SCCP, 2007).

Eye Irritation

Only limited data are available. The chemical at a 2 % concentration was slightly irritating to the eyes of rabbits. Therefore, the chemical may be an eye irritant at higher concentrations.

The chemical (0.1 mL of a 2 % solution) was applied to one eye each of three New Zealand White rabbits (OECD TG 405). The eyes were not rinsed after application and were examined at 1, 24, 48 and 72 hours, and seven days post exposure. The average scores for conjunctival redness and chemosis were given as grade 1. The effects were reversible within seven days. The test substance was reported to slightly irritate the eyes of rabbits (CIR, 2008).

Sensitisation

Skin Sensitisation

The chemical is not considered to be a skin sensitiser.

In a local lymph node assay (LLNA), groups of female CBA/J mice were topically treated with 0.25 µL of the chemical at 1, 2.5, 5, 10 and 25 % concentrations once a day for three days (OECD TG 406). The lymphoproliferative response, determined by the incorporation of (3H)- methyl thymidine, did not reach the stimulation index (SI) threshold of three in any treatment group (SCCP, 2007).

Repeated Dose Toxicity

Oral

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

In a 28-day oral gavage study in rats, at doses of 0, 100, 300 or 1000 mg/kg bw/day, a no observed adverse effect level (NOAEL) of 100 mg/kg bw/day was reported, based on slightly lower body weight gain in males at 300 mg/kg bw/day (SCCP, 2007). Effects observed at the highest concentration included a slight increase in cholesterol levels, increased liver weights in both sexes, and slight to moderate diffuse or centrilobular hepatocellular hypertrophy attributed to possible enzyme induction. No mortality occurred during the study.

In a 90-day oral gavage study in rats, at doses of 0, 25, 100 or 400 mg/kg bw/day, a NOAEL of 25 mg/kg bw/day was reported (SCCP, 2007). Effects observed at 100 mg/kg bw/day included slight lymphoid depletion. At the highest concentration, rats showed excessive salivation and increased water consumption, swollen abdomen, dehydration and signs of poor clinical condition, as well as litter staining; ophthalmological effects (yellow staining of the fundus in all animals and subcapsular, anterior cortical and total opacification of the lens in 6/10 males and 2/10 females); reduced average body weight gain (-40 % and -28 % compared with controls for males and females, respectively); and histopathological changes in some animals (including slight to moderate centrilobular hepatocyte hypertrophy and lymphoid depletion in the thymus). There were no mortalities during the study period.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the negative results reported for all in vitro genotoxicity studies, the chemical is not considered to be genotoxic.

The chemical gave negative results in several in vitro tests for gene mutation and clastogenicity (SCCP, 2007; CIR, 2008):

- bacterial gene mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2uvrA, with or without metabolic activation and at up to 5000 µg/plate;
- chromosome aberration test (non-guideline study similar to OECD TG 473) in Chinese hamster ovary (CHO) cells up to 2500 µg/mL concentration with or without metabolic activation; and
- a micronucleus assay (OECD TG 487) in human lymphocytes from two healthy, non-smoking male volunteers up to 1400 µg/mL with and without metabolic activation.

No in vivo genotoxicity data were available.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemical. Based on the available genotoxicity data, the chemical is not considered to be carcinogenic.

Experimental in vitro genotoxicity data (see **Genotoxicity**) show that the chemical is not considered to be genotoxic. No in vivo genotoxicity data are available. However, Quantitative Structure-Activity Relationship (QSAR) modelling using OASIS–TIMES resulted in positive predictions for both in vitro and in vivo genotoxicity. However, it should be noted that the chemical was out of the applicability domain of the models. If a prediction is out of the applicability domain of the model, it indicates that there is a greater uncertainty about the reliability of the models, since the performance statistics of the data in the model may not be applicable to the chemical. Thus, QSAR model predictions were considered not to outweigh the negative test results for genotoxicity within the weight of evidence analysis of the carcinogenic potential of the chemical.

Nitroaniline derivatives can be metabolically activated to reactive electrophiles as an initial step in a carcinogenic mechanism of action. This usually involves the activation of N-hydroxylamine metabolites with enzymatic reaction and eventual formation of pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions can covalently bind to DNA, provided that they are sufficiently stable to not undergo further reactions. The stability of the nitrenium ions is correlated with mutagenicity, for example in an Ames test with metabolic activation (Benigni & Bossa, 2011). For the chemical, the Ames test results were negative, indicating a lower likelihood of carcinogenic potential. Metabolic activation from the nitrenium ion intermediate would also result in oxidation of the hydroxyethyl group to a carboxylate group, which has been postulated to reduce the stability of the nitrenium ion and thus reduce the mutagenic potential of the chemical.

Reproductive and Developmental Toxicity

The chemical is not considered to have reproductive or developmental toxicity.

In a reproductive and developmental toxicity study (OECD TG 414), four groups of 20 pregnant females SD (Crl CD(SD)BR) rats were orally dosed with the chemical at 0, 100, 250 or 750 mg/kg bw/day on gestation days (GD) 6–15 (CIR, 2008). No mortality or abortion occurred during the study. The maternal effects in the rats included a transient decrease in body weight gain (observed at 250 and 750 mg/kg bw/day from GD 6–9) and decreased food consumption (-18 % compared with the control group) at 750 mg/kg bw/day. Neither embryonic nor teratogenic effects were observed at any dose level. A NOAEL of 100 mg/kg bw/day for maternal toxicity and 750 mg/kg bw/day for developmental toxicity were established (CIR, 2008).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects—acute toxicity from oral exposure.

The data are lacking for acute or repeated dose dermal and inhalation toxicity. Only limited data are available for eye and skin irritation. The chemical may cause slight eye irritation at 2 % concentration.

Public Risk Characterisation

The chemical is reported to be used in semi-permanent hair dye preparations in Australia.

The Cosmetic Ingredient Review (CIR) Expert Panel concluded that this chemical is safe for use in hair dyes at concentrations up to 0.15 % (CIR, 2008). The European Union (EU) has restricted the use of this chemical to a maximum of 0.15 % in ready-for-use non-oxidative hair dye products.

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

Currently, there are no restrictions in Australia on using this chemical in cosmetics or hair dyes. Although the public may be exposed to the chemical through its use in hair dyes, given that low hazards were identified with the chemical (acute oral toxicity and only mild eye irritation at 2 % concentration) and the expected low concentrations in hair dyes, the chemical is considered not to pose an unreasonable risk to public health.

Occupational Risk Characterisation

Given the critical health effects (acute oral toxicity and lack of data for acute or repeated dose dermal and inhalation toxicity), the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical 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 appropriate controls.

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

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2014).

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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	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 instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, ocular and inhalation 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 which may minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;

- 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 assist with meeting 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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