1,2-Propanediol, 3-[3-(methylamino)-4-nitrophenoxy]-: Human health tier II assessment

30 June 2017

CAS Number: 80062-31-3

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.

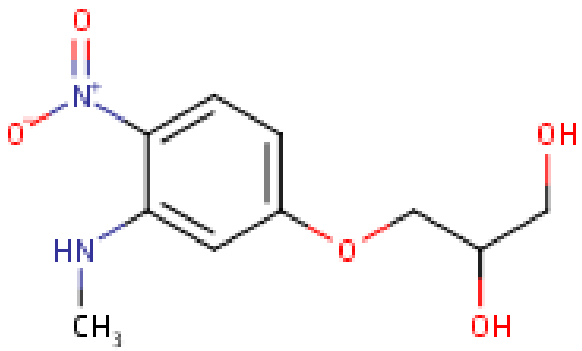
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-nitro-5-glyceryl methylaniline 3-(3-(methylamino)-4-nitrophenoxy)-1,2-propanediol
Structural Formula	
Molecular Formula	C10H14N2O5
Molecular Weight (g/mol)	242.23
Appearance and Odour (where available)	odourless yellow powder
SMILES	c1(N(=O)=O)c(NC)cc(OCC(O)CO)cc1

Import, Manufacture and Use

Australian

The chemical is reported to be used in semi-permanent hair dyes in Australia (NICNAS, 2007).

International

The following international uses have been identified through: Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the Scientific Committee On Cosmetic Products And Non-Food Products Intended For Consumers (SCCNFP, 2003) and the Scientific Committee for Consumer safety (SCCS, 2012), previously Scientific Committee on Consumer Products (SCCP, 2009).

The chemical has reported cosmetic use in semi-permanent hair dyes (CosIng) at a maximum concentration of 1 % (SCCP, 2009).

No other uses, industrial or non-industrial, have been reported.

Restrictions

Australian

No known restrictions have been identified.

International

Using the chemical in cosmetics in the European Union is subject to the restrictions described in EU Cosmetic Regulation Annex III/281.

This chemical may be used in oxidative and non-oxidative hair dye products at a maximum final concentration of 0.8 % and 1 %, respectively (CosIng). The following restrictions also apply:

- 'Do not use with nitrosating agents.
- Maximum nitrosamine content: 50 µg/kg.
- Keep in nitrite-free containers.'

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

Only limited information is available. Toxicokinetic behaviour of the chemical is not known, but in vitro studies reported that dermal absorption is expected to be low.

In a in vitro percutaneous absorption study, following the Organization for Economic Cooperation and Development Test Guideline (OECD TG) draft 428 (2000), a hair dye formulation containing the chemical at 0.9 % was tested on 20 human dermatomed skin samples. A dose of 20 mg/cm^2 of hair dye formulation was applied to the skin samples for 30 minutes. Most of the applied dose was not absorbed through the skin layers. The mean penetration (amount recovered in the receptor fluid) was 0.27 µeq/cm^2, equivalent to 0.13 % of the applied dose. About 0.11 % of the applied dose was absorbed in the epidermis and dermis. Therefore, a total of 0.24 % of the applied dose was considered as absorbed (SCCP, 2009).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) is between 1000 and 2000 mg/kg bw, warranting hazard classification.

In an acute oral toxicity study following OECD TG 401, Sprague-Dawley (SD) rats were administered the chemical as a single dose at 1000 or 2000 mg/kg bw. The median lethal dose (LD50) was estimated to be between 1000 (no mortality observed) and 2000 mg/kg bw (90% mortality) (SCCNFP, 2003).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Only limited information is available. The chemical is not irritating to the skin at concentrations up to 1 %.

In a skin irritation study following OECD TG 404, three New Zealand White (NZW) male rabbits were exposed to a suspension of the chemical at 1 % in 1,2-propanediol under semi-occlusive patch for four hours. No oedema was observed in any of the treated animals. Erythema could not be evaluated because of the red colouration of the skin (SCCNFP, 2003).

Eye Irritation

Only limited information is available. The chemical is slightly irritating to the eye at concentrations up to 1 %.

In a eye irritation study following OECD TG 405, three NZW male rabbits were exposed to a suspension of the chemical at 1 % in 1,2-propanediol, instilled into the left eye of each animal. One hour after instillation, slight redness of the conjunctivae and slight chemosis were observed. No effects were reported 24, 48 and 72 hours following instillation (SCCNFP, 2003).

Sensitisation

Skin Sensitisation

The chemical was found negative in a local lymph node assay (LLNA) and a guinea pig adjuvant study. Although concentrations used in both studies were too low to definitely make a conclusion on skin sensitisation, the chemical is not expected to be a strong skin sensitiser, as no effects were observed at doses up to 10 %.

In a LLNA following OECD TG 429, groups of female CBA/J mice (n= 4/group) were exposed to the chemical at concentrations of 0, 0.5, 1, 2.5, 5 or 10 % in dimethylformamide (DMF). The chemical was applied topically behind the ear of each animal for three consecutive days. Stimulation index (SI) remained <3 at all concentrations tested; therefore, the estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) was >10 %. The SCCP stated that the concentrations used were too low to definitely conclude on skin sensitisation (SCCP, 2009; SCCS, 2012).

In a non-guideline adjuvant study, groups of Albino Hartley guinea pigs (n = 10/sex) were exposed to the chemical at 1 % in propylene glycol. After a first intradermal injection of Freund's complete adjuvant (FCA) on day 1 and a second on day 10, guinea pigs were exposed to ten topical applications of the chemical at 1 % in propylene glycol. Each application was under occlusive patch and left for 48 hours. Twelve days after the tenth application, animals were challenged with the same suspension under occlusive patch for 48 hours on an untreated area. Results did not show any skin reactions up to 48 hours after removal of the patch (SCCNFP, 2003).

Observation in humans

There is no available evidence that the chemical is sensitising in humans.

Repeated Dose Toxicity

Oral

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

In a subchronic toxicity study following OECD TG 408, groups of SD rats (n = 10/sex/dose) were administered the chemical by gavage at doses of 0, 50, 200 or 800 mg/kg bw/day for 90 days. Mortality occurred at the highest dose, in 7/10 males and 6/10 females. Sublethal signs of toxicity included vacuolated pancreatic cells, tubular nephrosis and vacuolated renal tubular cells in the kidneys. Clinical signs of toxicity included ptyalism (excessive secretion of saliva) at 200 and 800 mg/kg bw/day, piloerection, hunched back, hypokinesia (loss of muscle movement), swollen abdomen, emaciation, dehydration and half-closed eyes at the highest dose. A yellowish colouration of urine, tail and body extremities was observed at all doses. Bilateral yellowish

colouration of the fundus oculi (concave interior of the eye) was observed at 200 and 800 mg/kg bw/day, and bilateral opacity of the lens was observed at 800 mg/kg bw/day. All other signs of toxicity were observed at the highest dose only. They included enlarged kidneys with tubular nephrosis and/or vacuolated tubular epithelium, enlarged liver with no microscopic changes, enlarged adrenals with cortical cell vacuolation (observed in one male only), smaller thymus and spleen correlated with lymphoid depletion and discolouration of the glandular stomach mucosa due to erosion. Histopathological observations were vacuolated Langerhans islet cells in the pancreas and renal tubular epithelial cells, and tubular nephrosis in the kidneys, at 800 mg/kg bw/day. A no observed effect level (NOEL) of 50 mg/kg bw/day and a no observed adverse effect level (NOAEL) of 200 mg/kg bw/day were determined in this study (SCCP, 2009).

In a subacute toxicity study following OECD 407, groups of SD rats (n = 10/sex/dose) were given by gavage doses of the chemical at 0, 100, 300 or 1000 mg/kg bw/day for 30 days. No mortality was recorded during the study, except for one male in the high dose group, possibly due to a gavage error. Hypersalivation was observed at the highest dose in 2/10 males and 5/10 females. Absolute and relative liver weights were slightly increased at the highest dose, but haematological and histopathological observations showed no treatment-related effects. There was a colouration of the urine and fur in rats given 300 and 1000 mg/kg bw/day, and a discolouration of the eye in the mid-dose group (7/10 males and 4/10 females) and high-dose group (9/9 males and 9/10 females). No other treatment-related signs were reported. The SCCNFP concluded that a NOAEL of 100 mg/kg bw/day could be determined (SCCNFP, 2003).

Dermal

No data are available on the chemical. Given the expected low dermal asorption (see **Toxicokinetics** section) and lack of systemic toxicity following oral exposure (see **Repeat Dose Toxicity: Oral** section), the chemical is not expected to be harmful following repeated dermal exposure.

Inhalation

No data are available on the chemical.

Genotoxicity

Based on the available data, the chemical is not expected to be genotoxic. Although some in vitro studies showed potential for clastogenicity, only negative results were reported in vivo.

In vitro

- In a bacterial gene mutation assay, following the European Commission (EC) B14 guideline, the chemical was tested on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA at concentrations up to 5000 µg/plate. An increase in the number of revertant colonies was observed in TA1537 only, with and without metabolic activation, but these results were respectively considered as not significant and not reproducible. The chemical was considered to be not mutagenic in that study (SCCP, 2009).

- In a non-guideline bacterial gene mutation assay, the chemical was tested on *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 by direct plate incorporation method. Concentrations used were 10, 20, 50, 100, 250, 500, 1000, 2500 or 5000 µg/plate, with and without metabolic activation. The chemical was found negative in this study (SCCNFP, 2003).

- In a mammalian gene mutation assay following OECD TG 476, the chemical was tested in L5178Y mouse lymphoma cells for increasing mutations on *tk* locus, at concentrations up to 2420 µg/mL with or without metabolic activation. Without metabolic activation, biologically relevant increases were observed at the two highest doses, 2200 and 2420 µg/mL. A biologically relevant and concentration-dependent increase was observed with metabolic activation (SCCP, 2009).

- In another study following OECD TG 476, the chemical was tested in L5178Y mouse lymphoma cells for increasing mutations on *hprt* locus, at concentrations up to 2000 µg/mL with, or 2200 µg/mL without metabolic activation. The chemical was found negative in this study. Although statistically significant increases were observed at doses >1200 µg/mL with metabolic activation, they were not reproducible in a third experiment, thus considered as not relevant (SCCP, 2009).

- In a mammalian chromosome aberration test following OECD TG 473, the chemical was tested in Chinese hamster ovary (CHO) cells at concentrations up to 2420 µg/mL with or without metabolic activation. At the highest concentration, the chemical induced statistically and biologically significant increase in the number of cells with chromosome aberrations (SCCP, 2009; SCCS, 2012).

In vivo

- In a bone marrow micronucleus assay following OECD TG 474, Crl:CD1 mice (n = 5/sex/dose) were treated with a single oral dose of the chemical at 0, 250, 500 or 1000 mg/kg bw. Although systemic exposure was demonstrated with plasma concentration measures, the chemical did not induce micronuclei in bone marrow cells of treated mice. This result is supported by two other studies following OECD TG 474, in which the chemical was found negative at doses up to 2000 mg/kg bw in Swiss mice, but where there was no evidence of systemic exposure in the bone marrow (SCCP, 2009; SCCS, 2012).

- In an unscheduled DNA synthesis (UDS) test following OECD TG 486, Wistar rats (n = 4/dose) were treated with a single oral dose of the chemical at 0, 875 or 1750 mg/kg bw. Although systemic exposure was demonstrated by ruffled fur and stained urine observed at the highest dose, no changes in DNA synthesis (increase in nuclear grain count or percentage of cells in repair) were observed during the study (SCCS, 2012).

Carcinogenicity

No data are available on the chemical. Mechanistic predictions overall indicate that the chemical has a lower likelihood to be carcinogenic compared with other nitroaniline chemicals.

Based on quantitative structure-activity relationship (QSAR) predictions, the chemical contains structural alerts for genotoxic carcinogenicity (OECD QSAR Toolbox). Nitroaniline derivatives can be metabolically activated to reactive electrophiles as an initial step in a carcinogenic mechanism of action. This usually involves activating N-hydroxylamine metabolites and their enzymatic reaction, and eventually formation of the pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions covalently bind to DNA, provided that they are sufficiently stable to not undergo further reactions immediately. The stability of the nitrenium ion is correlated with mutagenicity, for example in an Ames test with metabolic activation (Benigni & Bossa, 2011).

However, the stability of the nitrenium ion depends on the type of substituents and the isomeric position of the reactive groups. In the case of the chemical, the amino group is attached in the ortho position to the nitro group, potentially causing steric hindrance and preventing the activation of N-hydroxylamine metabolites. Therefore, compared with other nitroaniline derivatives, this chemical has a lower likelihood of being a carcinogen.

Reproductive and Developmental Toxicity

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

In a prenatal development toxicity study following OECD TG 414, groups of SD female rats were treated with oral doses of the chemical at 0 (n = 36), 100 (n = 40), 300 (n = 33) or 1000 mg/kg bw/day (n = 34), during gestation days (GD) 6–15. Maternal signs of toxicity included coloured urine in all treated animals and slightly decreased body weight gain and food consumption at the highest dose. One high-dosed female showed nasal discharge, piloerection, ulcerated foci in the stomach and yellow colouration of stomach, liver, kidneys and skin. At 1000 mg/kg bw/day, one dead foetus was observed, and the number of foetuses with unossified metacarpals had increased, but the result was not considered significant. A NOAEL of 300 mg/kg bw/day for maternal toxicity and 1000 mg/kg bw/day for developmental toxicity were determined (SCCP, 2009; SCCS, 2012).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is acute toxicity from oral exposure.

Public Risk Characterisation

Although the public could be exposed to the chemical through potential cosmetic and domestic uses, given the low hazard of the chemical, the chemical is not considered to pose an unreasonable risk to public health.

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 health effects, 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 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

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.

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