3H-Pyrazol-3-one, 2,4-dihydro-5-methyl-2-phenyl-: Human health tier II assessment

27 October 2017

CAS Number: 89-25-8

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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.

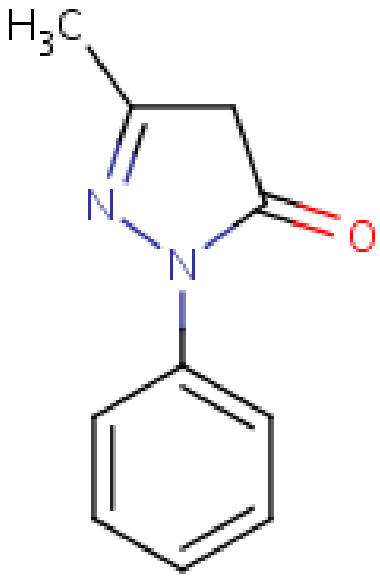
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-one 3-methyl-1-phenyl-2-pyrazolin-5-one 1-phenyl-3-methyl-5-oxo-2-pyrazoline methylphenylpyrazolone norphenazone
Structural Formula	
Molecular Formula	C10H10N2O
Molecular Weight (g/mol)	174.2
Appearance and Odour (where available)	White to light yellow odourless powder
SMILES	C1(=O)C=C(C)NN1c1ccccc1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the Substances in Preparations in Nordic Countries (SPIN) database; and international assessments from the National Cancer Institute (NCI) and the Scientific Committee on Consumer Products (SCCP).

The chemical has reported cosmetic use as a hair dye ingredient in oxidative hair dye products. The Food and Drug Administration (FDA) reported that in the 1980s, the chemical was used in a number of cosmetic products (about 125) at a concentration range of 0.1–1 % (CIR, 1992).

The chemical has reported domestic use in cleaning products (stain remover).

The chemical has reported site-limited use as an intermediate in the manufacture of various chemicals, including dyes.

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 III Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down; and
- 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.

Under these restrictions, this chemical may be used in oxidative hair dyes at a maximum concentration applied to hair of 0.25 %, after mixing under oxidative conditions (CosIng; Galleria Chemica).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemicals 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 the chemical in hair dye formulations was investigated in vitro and identified low percutaneous absorption. When administered via the oral route, the chemical was readily absorbed. Limited information is available on the metabolism and excretion of the chemical.

In an in vitro percutaneous study, an oxidative hair dye formulation containing the chemical at 0.5 % together with para-phenylenediamine (PPD) was tested using eight human skin samples from seven donors. After mixing with the developer, the final concentration of the chemical applied to the skin was 0.25 %. A mean amount of 0.56 % (0.31 µg/cm^2) of the applied dose was found in the receptor fluid within 24 hours post-exposure. The majority of the applied dose (92 %) was rinsed off the skin surface (SCCP, 2006).

In a second experiment, a non-oxidative hair dye formulation containing the chemical at 0.25 % was tested on 12 humans skin samples from seven donors. A mean amount of 2.92 % (1.6 µg/cm^2) was found in the receptor fluid within 24 hours post-exposure. The majority of the applied dose (96 %) was rinsed off the skin surface (SCCP, 2006).

In a subchronic oral toxicity study (see **Repeat Dose Toxicity: Oral** section), the chemical was administered to Sprague Dawley (SD) rats at doses of 0, 20, 100 or 500 mg/kg bw/day. The chemical was detected in the plasma at all doses. Plasma levels after the first dosing were comparable with the levels at the end of the study (13 weeks). Maximum concentration level (Cmax) was reached 30 minutes following administration. Systemic exposure values were reported to be 4.3 µg.h/mL in males and 15.1 µg.h/mL in females at 20 mg/kg bw/day. The values were reported to increase with the doses (SCCP, 2006).

The chemical is reported to be excreted as a glucuronide conjugate in humans, and sulfate conjugate in rats (CIR, 1992).

Acute Toxicity

Oral

The chemical has low acute toxicity following oral exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bw.

In an acute oral study conducted according to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 401, SD rats (n = 5/sex) were administered a single dose of 2000 mg/kg bw in three types of vehicles: methylcellulose (group 1), carboxymethylcellulose (group 2) or propylene glycol (group 3). Mortality rates resulted in 20 %, 30 % and 0 % of the animals in group 1, 2 and 3, respectively. Sublethal effects included hypoactivity or sedation, piloerection, ptosis

(drooping of the eyelids), reddish colouration of the extremities, dyspnoea and rhinorrhea (runny nose) in all treated rats (SCCP, 2006).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is a skin irritant, showing mild irritating effects in rabbits at low concentration. Although there is insufficient data to warrant hazard classification, the potential for skin irritation at low concentration of 1 % will be considered in the risk characterisation, as the chemical is used in cosmetic products.

In a study conducted according to the OECD TG 404, three New Zealand White (NZW) male rabbits were topically applied with a solution of 1 % of the chemical in propylene glycol for four hours under non-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours following exposure. Two rabbits had well defined erythema after one hour, which resolved within 24 hours. No other skin reactions were observed. The chemical was reported to cause a 'transient mild irritation' at 1 % concentration (SCCP, 2006).

Eye Irritation

Limited information is available for the chemical. The chemical at a low concentration produced no eye irritation in rabbits.

In a study conducted according to the OECD TG 405, three NZW male rabbits were exposed to the chemical at 1 % in propylene glycol, by instillation into the right eye. Reactions were recorded after 1, 24, 48 and 72 hours following exposure. No ocular reactions were observed in any of the treated animals (SCCP, 2006).

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive results seen in two local lymph node assays (LLNA). Moderate to strong sensitising effects were observed in these studies, warranting hazard classification.

Two LLNA were conducted according to the OECD TG 429 using CBA female mice (SCCP, 2006).

In the first study, the chemical in dimethylsulfoxide (DMSO) was dermally applied at concentrations of 1, 2.5, 5, 10 or 25 % (w/v) to groups of four CBA mice. A positive response in lymphocyte proliferation was measured at all doses tested, with stimulation indexes (SI) of 3.17, 9.15, 15.22, 12.18 and 9.81 with increasing concentrations. The estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) was determined to be 1 %. No signs of local irritation were observed.

In the second study, groups of four CBA mice were dermally applied concentrations of 0.1, 0.25, 0.5, 1 or 2.5 % of the chemical in DMSO. Stimulation indices of 1.67, 0.72, 2.77, 1.7 and 2.79 with increasing concentrations were reported. The EC3 was found to be >2.5 % in this experiment. No signs of local irritation were observed.

Repeated Dose Toxicity

Oral

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

In a subchronic toxicity study conducted according to the OECD TG 408, groups of SD rats (n = 10/sex/dose) were orally administered the chemical at doses of 0, 20, 100, or 500 mg/kg bw/day for 13 weeks. Clinical signs of toxicity included hypoactivity, half-closed eyes, rounded back and piloerection at the two highest doses. At the highest dose (500 mg/kg bw/day), food consumption and body weight gain were slightly decreased. Signs of regenerative haemolytic anemia were also observed, including decreased erythrocyte count and haemoglobin concentration, and increased mean cell volume and reticulocyte count, increased blood total and direct bilirubin concentrations, urinary traces of bilirubin and haemosiderosis (abnormal accumulation of iron) in the spleen. Lower blood glucose levels were observed in males at 100 and 500 mg/kg bw/day. Based on these observations, a no observed adverse effect level (NOAEL) of 20 mg/kg bw/day was established in the study. The SCCP considered that a NOAEL of 100 mg/kg bw/day and a no observed effect level (NOEL) of 20 mg/kg bw/day were more appropriate (SCCP, 2006).

In a dietary subchronic toxicity study, groups of rats (n = 5/sex/dose) were fed with 0, 2150, 3160, 4600, 6800, 10000, 14700 or 21600 ppm of the chemical in the diet for seven weeks, equivalent to 0, 194, 284, 414, 612, 900, 1323 and 1944 mg/kg bw/day, respectively (EFSA, 2012), followed by a one-week observation period. No mortalities were recorded, apart from one female in the control group. No signs of toxicity were observed. Based on slight decreased mean body weight gain in both male and female rats given 6800 ppm, the maximum tolerated dose to be considered in chronic studies was 5000 ppm (approximately 300 mg/kg bw/day) (see **Carcinogenicity** section) (NCI, 1978).

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 studies conducted in accordance with OECD test guidelines, the chemical is not considered to be genotoxic. Two in vitro genotoxicity tests showed positive results, but all in vivo tests were negative.

In vitro

The available in vitro studies gave both positive and negative results for the chemical (SCCP, 2006):

- In a bacterial gene mutation assay compliant with OECD TG 471, the chemical gave negative results in *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102, at concentrations up to 5000 µg/plate, with and without metabolic activation.
- In a mammalian cell gene mutation assay compliant with OECD TG 476, the chemical was tested on mouse lymphoma cells L5178Y (thymidine kinase (*tk*) locus) at concentrations of 0.313, 0.625, 1.25, 2.5, 5 or 10 mM (equivalent to 54, 109, 218, 435, 870 and 1740 µg/ml) in a first experiment; and 0.625, 1.25, 2.5, 5, 7.5 or 10 mM (equivalent to 109, 218, 435, 870, 1305 and 1740 µg/ml) in a second experiment. The chemical induced dose-related increase in mutant frequency, at all concentrations in the first experiment and at the three highest concentrations in the second experiment. Positive results were observed in the presence of metabolic activation only.

- In a mouse lymphoma assay compliant with OECD TG 476, the chemical was tested on mouse lymphoma cells L5178Y (*hprt* locus) at concentrations of 300, 600, 900, 1200, 1500 or 1740 µg/ml (equivalent to 10 mM) in the first experiment; and 200, 500, 800, 1100, 1400 or 1740 µg/ml (equivalent to 10 mM) in the second experiment. The chemical did not induce mutations with and without metabolic activation in both experiments.

- In a micronucleus test compliant with OECD TG 487, the chemical was tested in two experiments on cultured human lymphocytes. In the first experiment, concentrations were 187, 713 or 1740 µg/ml (equivalent to 10 mM) with metabolic activation and 234, 365 or 891 µg/ml without metabolic activation. In the second experiment, concentrations were 1114, 1392 or 1740 µg/ml (equivalent to 10 mM) with metabolic activation and 365, 570, 1114 or 1392 µg/ml without metabolic activation. Statistically signi`ficant, but not dose-related, increases in micronuclei were reported at most concentrations tested, only in the presence of metabolic activation. However, these increases were reported to be within the historical control range, and were therefore considered as not biologically relevant.

In vivo

The available in vivo studies gave negative results (SCCP, 2006):

- In a rat bone marrow micronucleus test compliant with OECD TG 474, the chemical was orally administered to SD rats (n = 5/sex/dose) in single doses of 0, 500, 1000 or 2000 mg/kg bw. While clinical signs of toxicity indicated systemic exposure, there was no increase in micronuclei incidence at any of the doses tested.

- In an unscheduled DNA synthesis (UDS) test compliant with OECD TG 486, the chemical was orally administered to male SD rats (n = 4/dose) in two experiments. In the first experiment, rats were dosed with 0, 250, 500, 1000 or 2000 mg/kg bw and euthanised 14 hours later. In the second experiment, rats were dosed with 0, 125, 250, 500 or 1000 mg/kg bw and euthanised two hours later. All rats given 2000 mg/kg bw died within 14 hours. There was no DNA damage at any of the doses tested.

Carcinogenicity

Based on the available data, the chemical is not expected to be carcinogenic.

In a carcinogenicity study in rats, groups of Fischer 344 (F344) rats (n = 50/sex/dose) were administered the chemical at 0, 2500 or 5000 ppm in the diet for 102 weeks, equivalent to 0, 125 and 250 mg/kg bw/day respectively (EFSA, 2012). No mortality or clinical signs of toxicity were associated with the chemical.

In treated male rats, a total of 88 primary tumours in 49/50 animals was observed, at low and high doses. These tumours included 17 and 13 malignant tumours, at low and high doses respectively, compared with 7/35 malignant tumours in the control group (19/20 animals). In males, the neoplastic lesions included leukemias, pituitary adenoma, adrenocortical adenoma and neuroendocrine tumour of the medulla of the adrenal glands, islet-cell adenomas in the pancreas or interstitial cell tumours in the testes.

In treated female rats, a total of 47 primary tumours were observed at low dose in 36/50 animals and 46 primary tumours at high dose in 25/50 animals, respectively, compared with 20 primary tumours in the control group in 12/50 animals. These tumours included six malignant tumours (6/47) in the low-dose group, eight (8/46) in the high-dose group, compared with five malignant tumours (5/20) in the control group. In female rats, neoplastic lesions included alveolar adenomas in the lungs, adenomas and carcinomas in the thyroid, fibroadenomas in the mammary gland and one endometrial stromal polyp in the uterus. However, there was no dose-relationship or statistical significance in the occurrences of individual tumours between treated and control rats of both sexes (NCI, 1978).

In a carcinogenicity study in mice, groups of B6C3F1 mice (n = 50/sex/dose) were administered the chemical at 0, 7500 or 15000 ppm in the diet for 102 weeks. There was no significant association between dosage and mortality, with an 80 % or more survival rate in all groups. A number of neoplastic and non-neoplastic lesions were observed in all treated groups, but there was no association or statistical significance between dosage and tumour incidence (NCI, 1978).

In both studies, study authors concluded there was no evidence of carcinogenic activity under the conditions tested (NCI, 1978).

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does not show specific reproductive or developmental toxicity. Developmental effects were only observed secondary to maternal toxicity.

In a prenatal development toxicity study conducted according to the OECD TG 414, mated female SD rats (n = 25/dose) were given oral doses of the chemical at 0, 40, 200 or 1000 mg/kg bw during gestation days (GD) 6–15. Maternal toxic effects were observed at the highest dose, including decreased body weight gain by 8 % compared with controls and one death of a non-pregnant female. Lower foetal weight and increased incidence of foetuses with reduced ossification were reported; however, these effects were associated with maternal toxicity. A NOAEL of 200 mg/kg bw was determined for both maternal and developmental toxicity (SCCP, 2006).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation.

The chemical is a slight skin irritant at a concentration of 1 %.

Public Risk Characterisation

In the absence of any regulatory controls for the chemical in Australia, the characterised critical health effect (skin sensitisation) has the potential to pose an unreasonable risk for the identified uses.

Currently, there are no restrictions in Australia on using this chemical in cosmetic products.

The risk could be mitigated by implementing concentration limits and restricting uses to limit dermal exposure. Similar overseas restrictions (New Zealand and the European Union—see **International restrictions**) on the use of this chemical in cosmetic products overseas, if applied into Australia, are considered appropriate to mitigate the risk.

Occupational Risk Characterisation

During product formulation, 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 effect, 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 a new entry to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to the Poisons Standard, and risks for workplace health and safety be managed through changes to the HCIS classification and labelling.

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

Given the risk characterisation, it is recommended that the chemical be included in the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) for use in cosmetic and domestic products to ensure appropriate labelling.

Matters to be taken into consideration include:

- the known use of the chemical in cosmetic products in Australia (in permanent and semi-permanent hair dyes), similar to use in cosmetic products overseas at concentrations up to 0.25 % (CosIng) ;
- the chemical being a skin sensitiser, as demonstrated in animal studies, although there is no epidemiological data showing cases of sensitisation in humans; and
- restrictions on the cosmetic uses overseas, and that the restrictions on the use of this chemical in cosmetic products in New Zealand and the European Union (see **International restrictions**) are considered appropriate to mitigate the risk.

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonised 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]
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)

[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:

- 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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