1H-Indole-2,3-dione: Human health tier II assessment

27 October 2017

CAS Number: 91-56-5

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.

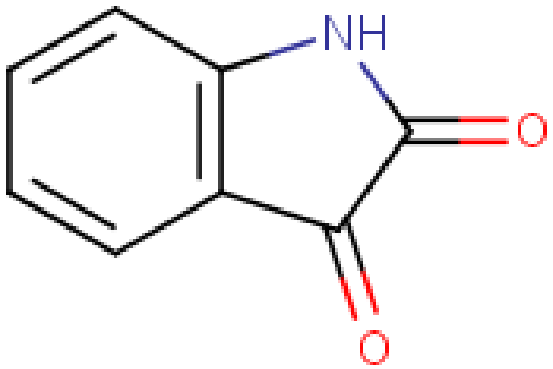
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	isatin tribulin 2,3-Indolinedione isotin
Structural Formula	
Molecular Formula	C8H5NO2
Molecular Weight (g/mol)	147.13
Appearance and Odour (where available)	orange crystalline powder
SMILES	C1(=O)C(=O)c2c(cccc2)N1

Import, Manufacture and Use

Australian

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

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

International

The following international uses have been identified through Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the European Commission Scientific Committee on Consumer Products (SCCP, 2005).

The chemical has reported cosmetic use as hair dye ingredient in non-oxidative hair dye products at final concentration of up to 1.6 % (SCCP, 2005).

The chemical has reported site-limited uses, including as an intermediate in manufacture of vat dyes.

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down; and
- Association of South East Asia Nations (ASEAN) Cosmetic Directive Annex III—Part I List of substances which cosmetic products must not contain except subject to restrictions and conditions.

Under these restrictions, the chemical may be used in non-oxidative hair dye products at a maximum concentration of 1.6 % when applied to hair (CosIng; Galleria Chemica).

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

The dermal absorption of the chemical in hair dye formulations was investigated in vitro and identified as low percutaneous absorption.

In an in vitro percutaneous study, a hair dye formulation containing the chemical at 1.6 % in an oxidative formulation (with 40 % hydrogen peroxide solution) and an aqueous formulation without hydrogen peroxide was tested using eight human abdominal skin samples from four different donors. A mean amount of 3.87 ± 1.70 µg/cm^2 for oxidative formulation and 2.39 ± 0.84 µg/cm^2 for aqueous formulation of the applied dose were found in the receptor fluid within 24 hours post-exposure (SCCP, 2005).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from an animal test following oral exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bw.

In an acute oral toxicity study, groups of Crl:CD (SD) BR strain rats (n=5/sex/group) were administered a single dose of 2000 mg/kg bw by gastric gavage. Three animals were euthanised in extremis at 5 hours or 24 hours post dosing. Sublethal effects observed on the day of dosing included hypoactivity, laboured respiration, piloerection and pale extremities. No other treatment-related adverse effects were observed. An LD50 of >2000 mg/kg bw was determined (SCCS, 2005).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical was not found to be a skin irritant.

In a skin irritation study conducted according to OECD Test Guideline (TG) 404, New Zealand White (NZW) rabbits (n=3) were dermally applied the chemical (99.1 % purity) on a shaved, clipped dorsal area, under semi-occlusive patch for four hours. After four hours, the patch was removed and the application site was cleaned and observations were made at 1, 24, 48 and 72 hours. Yellow to slight orange staining was seen in 2/3 animals at all observation times. No skin reactions were reported (SCCS, 2005).

Eye Irritation

The chemical was not found to be an eye irritant.

In an eye irritation study (OECD TG 405), female NZW rabbits (n=3) were administered 0.1 mL of the chemical (99.1 % purity) in the conjunctival sac of the right eye. Observations were made at 1, 24, 48 and 72 hours post-instillation. Orange staining in the eyes was observed for up to 24 hours. No signs of ocular irritation were reported (SCCS, 2005).

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive results in guinea pig maximisation test (GPMT) and local lymph node assay (LLNA). The chemical was moderately to strongly sensitising in these studies, warranting hazard classification (see **Recommendation** section).

In a guinea pig maximisation test (GPMT), conducted according to OECD TG 406, the chemical was tested for skin sensitisation potential in female Dunkin-Hartley guinea pigs (n=20). In the induction phase, the animals received the chemical in propylene glycol. On day 8, occlusive patches containing 25 % w/v of the chemical in propylene glycol for 48 hours was used as topical induction. On day 22 (14 days after the topical induction), a challenge at 25 % w/v of the chemical in propylene glycol resulted in all treated animals showing positive response at 48 hours. Scores were not reported. The authors concluded that the chemical was an extremely potent skin sensitiser (SCCS, 2005).

In a Buehler test, the chemical at 25 % in propylene glycol was applied topically to the left shoulder of 20 female Dunkin-Hartley guinea pigs for six hours under occlusive conditions, during induction. The treatment was repeated twice on days 8 and 15 of the study. After two weeks of rest period, topical challenge doses of the chemical at 10 % and 25 % in propylene glycol were applied on the right and left flanks, respectively. Orange/red staining of the test sites made the observation difficult and the authors concluded that there was no evidence of contact allergy (SCCS, 2005). The study is regarded as inconclusive due to the difficulty in assessing the test sites for skin sensitisation effects.

In two LLNA assays conducted according to OECD 429, the chemical in dimethylformamide (DMF) was dermally applied at concentrations of 1, 2.5, 5, 10 or 25 % to groups of female CBA/J mice (n=56). In the first assay, a positive response in lymphocyte proliferation was measured at all doses, with stimulation indices (SI) of 5.3 to 15.6 with increasing concentrations. The estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) was less than 1 %. No signs of local irritation were observed. In the second assay, the SI values were close to 1 for all concentrations tested, except at 2.5 %, where the SI value was 3. The EC3 was calculated to be close to 2.5 %. The authors concluded that the chemical was a moderate sensitiser (SCCS, 2005).

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 13-week subchronic toxicity study, Crl:CD (SD) BR strain rats (n=10/sex/dose) were orally administered the chemical at doses of 0, 10, 50 or 250 mg/kg bw/day, seven days/week for 13 weeks. Four mortalities were recorded before the end of the study. Sublethal effects included hair loss, scabbing and generalised yellow staining of the fur. At 250 mg/kg bw/day, orange

peri-buccal staining was seen from day 16. Significant dose-related decreases in the red blood cell count in both sexes were reported. Males dosed at 250 mg/kg bw/day had significant increases in blood triglyceride and inorganic phosphate levels, increased urine volume, and elevated absolute and relative heart and relative liver weight. Minor abnormalities in histopathology were reported in both sexes, but were considered to be non-treatment related. A no observed adverse effect level (NOAEL) of 50 mg/kg bw/day was determined (SCCS, 2005).

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 (TG), the chemical is not considered to be genotoxic. One in vitro genotoxicity test indicated positive results, but all in vivo tests were negative.

In vitro studies

In a bacterial gene mutation assay conducted according to OECD TG 472, the chemical gave negative results in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; and *Escherichia coli (E.coli*) at concentrations up to 5000 µg/plate, with and without metabolic activation (Bacani et al, 2011; SCCS, 2005).

In an in vitro chromosome aberration test (OECD TG 473), the chemical induced a significant increase in frequency of aberrations, with and without activation at concentrations of 1.3–729 µg/mL (Bacani et al, 2011; SCCS, 2005).

In vivo studies

In a mouse bone marrow micronucleus test (OECD TG 474), the chemical was orally administered to CD1 mice (n=5/sex/dose) as a single dose at concentrations of 0, 125, 200 or 300 mg/kg bw/day. While signs of systemic toxicity were observed, no increases in the number of micronucleated cells were reported (Bacani et al, 2011; SCCS, 2005).

In an unscheduled DNA synthesis (UDS) test, the chemical was administered to male Wistar rats (n=8/dose) by gavage at doses of 0, 150 or 1500 mg/kg bw/day. One animal died at 1500 mg/kg bw/day. All treated animals showed piloerection and apathy after dosing. No DNA damage was observed at any of the doses tested (Bacani et al, 2011; SCCS, 2005).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

The chemical does not cause specific reproductive or developmental toxicity, based on the limited data available. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a prenatal developmental toxicity study conducted according to OECD TG 414, groups of female SD rats (n=24/dose) were given oral doses of the chemical at 0, 50, 150 or 500 mg/kg bw/day during gestation days (GD) 6–15. Salivation and hair loss were reported in a number of treated animals. Weight gain was significantly reduced at 500 mg/kg bw/day on GD 6–9. No significant changes in the mean number of corpora lutea, implantation sites, post-implantation loss, live foetuses, sex distribution

and mean foetal bodyweights were reported. Minor skeletal abnormalities were seen in foetuses of dams treated at 50 and 150 mg/kg bw/day, but the authors considered these effects as not treatment-related. A NOAEL of 150 mg/kg bw/day for maternal toxicity and a NOAEL of 500 mg/kg bw/day for development toxicity were determined (SCCS, 2005).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation.

Public Risk Characterisation

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

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

The risk could be mitigated by implementing concentration limits and restricting uses to limit dermal exposure. Overseas restrictions (European Union and the ASEAN—see **International restrictions**) on the use of this chemical in cosmetic products, if applied in 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 cosmetic and domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to 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

Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemical is used in domestic and cosmetic products. Due to the toxicity profile of the chemical and the concentrations reported to be potentially in use (1.6 %), it is recommended that the chemical be included the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) to ensure appropriate labelling for use in hair dyes. 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 1.6 % (SCCP, 2005);
- 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 the European Union and ASEAN (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 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]
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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Last update 27 October 2017

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