# 2-Naphthalenamine, N-phenyl-: Human health tier II assessment

**12 September 2013**

## CAS Number: 135-88-6



## 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.

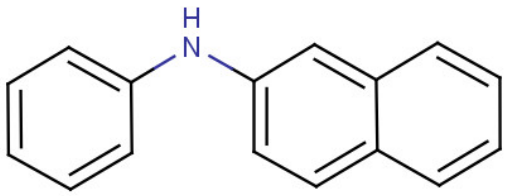
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

# Chemical Identity

| | |
|---|---|
| Synonyms | phenyl-beta-naphthylamine<br>N-2-naphthylaniline<br>N-Phenyl-beta-naphtylamine |
| Structural Formula |  |
| Molecular Formula | C16H13N |
| Molecular Weight (g/mol) | 219.29 |
| Appearance and Odour (where available) | White to yellow crystals or grey tan flakes or powder. |
| SMILES | c12c(cc(Nc3ccccc3)cc1)cccc2 |

# Import, Manufacture and Use

## Australian

The Australian industrial use, commercial use in jet oil formulation, was reported under previous mandatory and/or voluntary calls for information (NICNAS, 2008).

### International

The following international uses have been identified through the International Agency for Research on Cancer (IARC); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; and the US National Library of Medicine's Hazardous Substances Data Bank—HSDB.

The chemical has reported commercial use including:

- as an antioxidant in rubber processing to increase heat and crack-resistance;
- as an antioxidant in greases and lubricating oils;
- as a stabiliser in electrical-insulating silicone enamels; and
- as a component of rocket fuels.

The chemical has reported site-limited use including:

- dye production, including C.I. Acid Blue 98.

The chemical has been reported to have non-industrial use as a component in surgical plasters.

## Restrictions

### Australian

No known restrictions have been identified.

### International

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

- EU Cosmetic Directive 76/768/EEC Annex II—List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- US FDA Indirect food additives: adhesives and components of coatings—substances for use only as components of adhesives—may be used as a component in adhesives used in food packaging provided it does not contain 2-naphthylamine; and
- US FDA List of 'indirect' additives used in food contact substances.

## Existing Work Health and Safety Controls

### Hazard Classification

Carc. Cat. 3; R40

Xi; R36/38 R43

### Exposure Standards

#### Australian

Under the HSIS, it is not currently possible to assign an appropriate exposure standard for this chemical. Given its carcinogenic potential, exposure should be controlled to the lowest practicable level.

#### International

No exposure standards were identified.

## Health Hazard Information

### Toxicokinetics

The purity of the tested chemical, and especially the amount of 2-naphthylamine contamination, can affect experimental results relating to the demonstration of 2-naphthylamine excretion in an animal species. Researchers concluded that 2-naphthylamine was generated from metabolism of the chemical at such low levels that the potential dephenylation of the chemical in vivo does not produce carcinogenic risk (NRC, 2004).

### Acute Toxicity

#### Oral

Based on the available information for this chemical, no hazard classification for acute oral toxicity is recommended.

The chemical was reported to have low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats is 8,730 mg/kg bw. Observed sublethal effects included unspecified vascular changes in the liver, lungs, and brain as a result of venous congestion in rats administered with this dose (NAS, 2004).

#### Dermal

No data are available.

#### Inhalation

No data are available.

### Corrosion / Irritation

#### Skin Irritation

The chemical is currently classified as hazardous with the risk phrase 'Irritating to skin' (Xi,R38) in HSIS (Safe Work Australia). No data are available to recommend removal of the current classification.

### Eye Irritation

The chemical is currently classified as hazardous with the risk phrase 'Irritating to eyes' (Xi,R36) in HSIS (Safe Work Australia). No data are available to recommend removal of the current classification.

## Sensitisation

### Skin Sensitisation

The chemical is currently classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (Xn,R43) in HSIS (Safe Work Australia). There are human data to support this classification (IARC, 1978).

### Observation in humans

Exposure to the chemical was associated with skin sensitisation in humans. Leucoplakia (growth of keratin on the skin or on mucous membranes), acne and hypersensitivity to sunlight were observed in 36 workers exposed for prolonged periods to the chemical (IARC, 1978). Sensitisation of skin in employees who work with rubber was associated with exposure to rubber and its additives (HSDB).

## Repeated Dose Toxicity

### Oral

Considering the lowest observed effect levels (LOELs) available from 14, 30 and 90-day studies (200–17000 mg/kg bw/d) in rats and mice and based on the treatment-related effects reported in various repeated dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated oral exposure. No observed adverse effect levels (NOAELs) ranged from 600 mg/kg bw/d in female rats to 1400 mg/kg bw/d in male mice, with adverse effects above these levels mainly occurring as nephropathic lesions in the kidneys. Other effects seen at these high doses included decreased body weight, increased liver-to-body weight ratios, gastrointestinal disturbance, immunotoxicity, reproductive toxicity and haematopoietic irregularities (NRC, 2004).

Oral chronic toxicity studies are reported in the carcinogenicity section.

### Dermal

No data are available.

### Inhalation

There is limited evidence of repeated dose toxicity by inhalation, as study details were lacking. Rats inhaling 900 mg/L of the chemical for 14 days experienced weight loss, slight erythrocytopaenia, and pulmonary emphysema (HSDB).

## Genotoxicity

Based on the available data, the chemical is not considered to be mutagenic or genotoxic.

The chemical was evaluated as having a structural alert for DNA reactivity (potential genotoxic carcinogenicity) because of its carcinogenic subunit—2-naphthylamine. The NAS (2004) reported the chemical as a rather weak clastogen and mutagen following a battery of in vitro tests undertaken by the National Toxicology Program using elevated concentrations, extended exposure times and in the presence of metabolic activation. Tests included bacterial reverse mutation assays, in vitro mammalian gene mutation and sister chromatid exchange assays.

### Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40) in HSIS (Safe Work Australia). While the available data do not support this classification, given the uncertainties in the data and the potential for this chemical to metabolise to a prohibited carcinogen, there is insufficient evidence to support removing this classification.

A National Toxicology Program study reported in NAS (2004) found no evidence of carcinogenicity in male or female rats fed a maximum dose of 225 and 262 mg/kg bw/day for two years. The absence of carcinogenicity in rats in that study might be related to the limited ability of this species strain to metabolise the chemical to the carcinogen 2-naphthylamine or its carcinogenic metabolites; however, metabolites were not evaluated in the study. In another rat study reported in NAS (2004), the refined chemical was administered by gavage to male rats at 160 and 320 mg/kg bw for 12 months. Twenty-seven of 57 dosed rats developed carcinomas of the lungs, kidneys, prostate and pancreas compared with 6/43 controls that developed these tumours. The chemical in the former study was administered through an ad libitum (freely available) diet as opposed to gavage in the latter study, thus differences in absorption characteristics may have led to different toxicological consequences following ingestion.

In addition, other animal studies with rats, dogs and mice found either no or equivocal evidence of carcinogenicity (NAS, 2004).

Epidemiological findings were not clear due to confounding by the presence of other chemicals (NAS, 2004; IARC, 1978).

### Reproductive and Developmental Toxicity

There is limited evidence of reproductive toxicity in one rat study. However, classification was not considered as study details were not available.

In the study, reported in NAS (2004), impaired reproductive function, indicated by desquamation of spermatogenic epithelium, was reported in white male rats fed diets containing the industrial-grade chemical at 100 mg/kg for 18 months. When dosed males were mated with healthy females, the resulting embryos perished twice as often as embryos resulting from mating between control males and healthy females. Further quantitative or qualitative descriptions of reproductive toxicity were not presented.

## Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation is carcinogenicity. The chemical may also cause harmful effects following exposures such as skin and eye irritation or skin sensitisation.

### Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

### Occupational Risk Characterisation

Based on the available data, the hazard classification in HSIS is considered appropriate.

During product formulation, dermal, ocular and inhalation 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. For example, the chemical is detectable when 1,3-butadiene rubber is heated to temperatures of 220 °C (IARC, 1978).

Given the critical systemic long-term and local health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation 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

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

## Regulatory Control

### Public Health

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

### 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] |
|---|---|---|
| Irritation / Corrosivity | Irritating to eyes (Xi; R36)*<br>Irritating to skin (Xi; R38)* | Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) |
| Sensitisation | May cause sensitisation by skin contact (Xi; R43)* | May cause an allergic skin reaction - Cat. 1 (H317) |
| Carcinogenicity | Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)* | Suspected of causing cancer - Cat. 2 (H351) |

[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 industry

***Control measures***

Control measures to minimise the risk from oral/dermal/ocular/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 closed systems or isolating operations;
- 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 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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