# 2-Thiazolamine, 5-nitro-: Human health tier II assessment

**30 June 2017**

## CAS Number: 121-66-4



## 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.

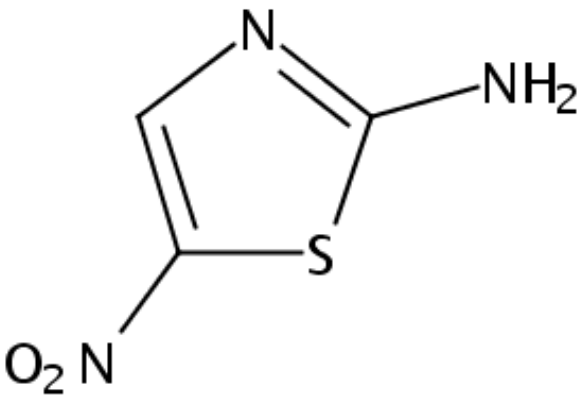
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

# Chemical Identity

| | |
|---|---|
| Synonyms | thiazole, 2-amino-5-nitro-<br>enheptin<br>amnizol soluble<br>entramin<br>2-amino-5-nitrothiazole |
| Structural Formula |  |
| Molecular Formula | C3H3N3O2S |
| Molecular Weight (g/mol) | 145.14 |
| Appearance and Odour (where available) | Orange-yellow fluffy powder or a brown chunky powder. Slightly bitter taste. |
| SMILES | C1(N(=O)=O)=CN=C(N)S1 |

# Import, Manufacture and Use

## Australian

No specific Australian use, import, or manufacturing information has been identified.

### International

The following international uses have been identified through the Organisation for Economic Co-operation and Development (OECD) High Production Volume chemical program (OECD HPV), the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US National Toxicology Program (NTP); the International Agency for Research on Cancer (IARC); Sonnenhurg et al., 2012; and PubChem.

The chemical has reported site-limited use as an intermediate in the manufacture of azo dyes.

The chemical has reported non-industrial use as a veterinary medicine.

## Restrictions

### Australian

No known restrictions have been identified.

### International

No known restrictions have been identified.

## 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

Thiazole and its derivatives are metabolised via oxidation of the heterocyclic atoms (sulfur and nitrogen) and the major metabolites are excreted in the urine as free or glutathione conjugates. Ring cleavage and ring carbon oxidation may also occur (European Food Safety Authority (EFSA), 2016).

The chemical has a logP value of 0.8 (PubChem), indicating that the chemical is rather hydrophilic. Therefore, it is expected that only a small proportion of a dermal dose would be absorbed through the skin.

## Acute Toxicity

### Oral

Limited data available for acute oral toxicity is not adequate for the hazard classification.

The reported median lethal dose (LD50) for the chemical in mice via oral route is 535 mg/kg bw (Schnitzer, 1963). No further study details are available.

### Dermal

No data are available.

### Inhalation

No data are available.

## Corrosion / Irritation

### Skin Irritation

Based on limited data available, the chemical is expected to be weakly irritating to skin.

The irritation potential of the chemical was determined in a loose-fit co-culture-based sensitisation assay (LCSA) that is capable of identifying the irritation potential of substances (Wanner et al., 2010). The irritation potential is based on the concentration which causes cell death of 50% (EC50) of dendritic cells in the co-culture. The chemicals with EC50 below 50 µmol/L are considered strongly irritating (Wanner et al., 2010). The EC50 value for the chemical was determined to be 126 µmol/L and therefore categorised as weakly irritating to the skin (Sonnenburg et al., 2012).

### Eye Irritation

No data are available.

## Sensitisation

### Skin Sensitisation

Based on limited data availability, the chemical is considered to be weak skin sensitiser.

The sensitising ability of the chemical was determined in a LCSA assay that is capable of identifying the sensitising potential of substances (Wanner et al., 2010). The assay addresses the third key event (dendritic cell activation) in the skin sensitisation adverse outcome pathway (AOP) (OECD, 2012) and is based on cell surface marker CD86 expression. The sensitising potential is categorised based on the concentration that induces a half-maximal increase in CD86 expression. The chemicals with EC50 above 100 µmol/L are considered not to be strong sensitisers (Wanner et al., 2010). The chemical had an EC50 value of 120 µmol/L and was therefore categorised as weakly sensitising to the skin (Sonnenburg et al., 2012).

The weak skin sensitisation potential is supported by the lack of skin sensitisation reactivity alerts on Toxtree v 2.6.6 modelling (Patlewicz et al., 2008) and lack of structural alerts for skin sensitisation using the knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus: 5.0.1 (Lhasa Limited).

## Repeated Dose Toxicity

### Oral

Only limited data are available.

In subchronic studies conducted in Fischer 344 (F344) rats and B6C3F1 mice, the chemical was administered in diet at concentrations of 375–4000 ppm and 30–500 ppm, respectively (equivalent to approximately 50–600 and 10–200 mg/kg bw/day). Significant decreases in body weight gain were reported in male and female rats and in female mice. Slightly enlarged thyroids were reported at high doses in rats. No effects were observed in mice (NTP, 1978).

In a non-guideline study, rats (no further details available) were fed a diet containing the chemical at concentrations of 0.06 to 0.1 %. The chemical was reported to have low toxicity, but the treated rats had larger thyroid glands and a lower accumulation of iodine 131 when compared to control rats (Shellabarger and Schatzlein, 1955; abstract only).

### Dermal

No data are available.

### Inhalation

No data are available.

## Genotoxicity

The available data from in vitro mutagenicity assays suggest that the chemical may be mutagenic but is insufficient to warrant hazard classification.

The chemical was determined to be mutagenic in the following in vitro assays:

- reverse mutation assay in *Salmonella typhimurium* strain TA100 at concentrations greater than 100 µg/plate with or without S9 metabolic activation;
- mutagenicity assay in *Escherichia coli* (OEHHA, 1999);
- fluctuation test in *Klebsiella pneumonia* (IARC, 1983); and
- the L5178Y mouse lymphoma cell forward mutagenesis assay with and without S9 (Myhr & Caspary, 1988).

The chemical was reported non-mutagenic in *S typhimurium* strains TA1535, TA1537, TA1538, and TA98 (IARC, 1983).

### Carcinogenicity

Based on the available data, the potential that the chemical is carcinogenic cannot be ruled out. While, the International Agency for Research on Cancer (IARC) has classified the chemical as 'Not classifiable as to its carcinogenicity to humans' (Group 3), the chemical was recently suggested to have carcinogenicity concern as an azo cleavage product from the textile dyes (Bruschweiler et al., 2014).

Weanling female Sprague Dawley (SD) rats (n=35) were administered with the chemical in the diet at a concentration of 1140 mg/kg for one week, 750 mg/kg from week two to week nine, 1000 mg/kg until the 46th week (total cumulative dose per rat = 4.6 g; equivalent to approximately 150 mg/kg bw/d). Control and dosed rats were fed the control diet until the end of the study at 66th week. Seven mammary fibroadenomas and one mammary carcinoma were observed in 8/35 of the treated rats and fibroadenomas in 2/39 of the controls. Treated animals also developed renal pelvis hyperplasia (6/35); renal pelvis transitional-cell carcinomas (2/35); and pulmonary alveolar-cell carcinomas (2/35) (IARC, 1983).

Rats (F344; n=50/sex/dose) were administered the chemical in the diet at concentrations of 300 or 600 mg/kg for 110 weeks followed by a week of the control diet. A dose-dependent trend in mortality was reported. Statistically significant increases in tumour and neoplasm incidences were observed including: malignant lymphomas, lymphocytic leukaemias in the low dose (15/50) and high dose (19/49) groups compared to the control group (11/50); and in the incidence of granulocytic leukaemia in males for the low dose (4/50) and high dose (9/49) groups compared to the control group (2/50). A dose-dependent trend was also observed in the incidence of pituitary chromophobe adenomas in females (19/45 controls; 29/47 low dose; 29/44 high dose). It was noted that the average incidence of pituitary gland tumours in historical control groups was 40% and 20.3% in females and males, respectively (NTP, 1978; IARC, 1983).

### Reproductive and Developmental Toxicity

Only limited data are available. The chemical has potential to be harmful to male reproductive organs. However, the data is not sufficient for classification.

The following non-guideline studies were performed in rats (Snair & Schwinghamer, 1960):

Male Wistar rats (n=12-20 /dose) were fed diets containing the chemical at 0, 0.033, 0.066 or 0.1 % (equivalent to approximately 16.5, 33 or 50 mg/kg bw/day) for 10 days. At the two highest doses, seminal vesicle and prostate weights were significantly reduced compared to control. No effect was reported on teste weights.

Female Wistar rats were (n=15/dose) were fed diets containing the chemical at 0, 0.1 or 0.2 % (equivalent to approximately 0, 50 or 100 mg/kg bw/day) for two weeks. The chemical caused a dose-dependent effect on the oestrous cycle with the treated females having extended dioestrus stage of the cycle. The effect on oestrous cycle was transient with all rats cycling normally at the end of the experiment. The body or the uterine weights were not affected.

Male Wistar rats (n=15/dose) were fed diets containing the chemical at 0 or 0.1 % concentration. The males were treated for seven days before mating with female rats. The treatment of males continued for four weeks. The chemical significantly reduced prostate and seminal vesicle weighs in treated males. Five weeks after the first mating day, the control males had sired 27 litters compared to 17 litters in the treatment groups. Also, at the end of the experiment, the total number of pups produced was lower in treatment group (222) compared to control group (273). These findings indicate potential effect on male fertility.

## Risk Characterisation

### Critical Health Effects

The critical health effect for risk characterisation is carcinogenicity, although this is not fully characterised. Additionally, the acute oral toxicity, reproductive toxicity and mutagenic potential of the chemical cannot be ruled out, and should be reviewed if further information becomes available.

### Public Risk Characterisation

The chemical could be used as intermediate in the manufacture of dyes (see ***Import, Manufacture and Use*** section) which may be used in tattoo inks and textile dyes, and it may then be regenerated by reductive cleavage of the azo dyes. The chemical was indicated as a potential aromatic amine cleavage product of concern from azo dyes (Bruschweiler et al., 2014). As such, further regulatory controls for public health may be determined as part of a Tier III assessment for 'Azo dyes that cleave to aromatic amines of potential toxicological concern'.

### Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation 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.

## NICNAS Recommendation

The chemical is recommended for a Tier III assessment as part of the assessment of 'Azo dyes that cleave to aromatic amines of potential toxicological concern' (NICNAS).

### Regulatory Control

#### Public Health

The need for regulatory control for public health will be determined as part of the Tier III assessment.

#### Work Health and Safety

The need for regulatory control for worker health will be determined as part of the Tier III assessment

### 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/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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;

- 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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 safety data sheets (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 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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