1H-Imidazole, 4-methyl-: Human health tier II assessment

21 April 2016

CAS Number: 822-36-6

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.

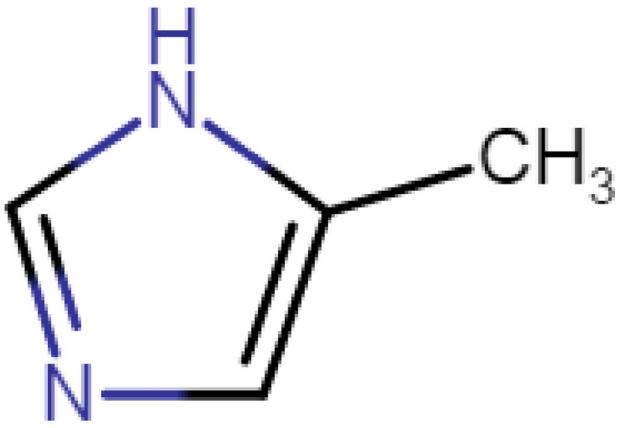
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4-methylimidazole 5-methylimidazole 4(5)-methylglyoxaline
Structural Formula	
Molecular Formula	C4H6N2
Molecular Weight (g/mol)	82.105
Appearance and Odour (where available)	Light yellow crystalline solid
SMILES	C1(C)=CNC=N1

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: Galleria Chemica; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (National Toxicology Program (NTP)).

The chemical has reported domestic use as a component in imidazole-phenoxyalkanal oven cleaners (NTP, 2007). However, the US Household Products Database does not indicate any domestic use of the chemical.

The chemical has reported commercial uses, including:

- as a crosslinking agent for epoxy resin hardeners;
- as a corrosion inhibitor for cooling water in heat-exchange apparatus; and
- for acid gas removal from hydrocarbon or synthesis gas.

The chemical has reported site-limited use, including:

- as an intermediate, starting material or component for manufacturing inks and paper dyes, photographic and photothermographic chemicals, and rubber.

The chemical has reported non-industrial use, including as a pharmaceutical intermediate (starting material for drugs and antiseptic agents).

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 Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

The toxicokinetics of the chemical in animals showed species differences.

The chemical was readily absorbed in rats following oral gavage. The peak plasma concentrations were reached at 0.5, 1.0 and 3.0 hours for doses 5, 50 and 150 mg/kg bw, respectively. Bioavailability was estimated to be 60–70 %, based on total urinary recovery. There was little to no metabolism observed, although the formation of one minor hydrophilic metabolite was identified in urine and plasma. Renal clearance appeared to be a saturable process at 50 mg/kg bw. Using a toxicokinetic model, an absorption half-life between 5–23 minutes, and an elimination half-life between one to eight hours was determined for rats administered a single oral dose of the chemical at 10–100 mg/kg bw (NTP, 2007; IARC, 2012; HSDB).

In sheep, ~50 % of an oral dose (20 mg/kg bw) of the chemical was absorbed in 27 minutes, with a peak plasma concentration at five hours following administration. Bioavailability was estimated to be 69 %, based on available plasma levels, and the biological half-life was 9.37 hours. Recovery of the unchanged parent compound in the urine was only 0.07 mg/kg bw. Metabolites were unable to be detected (NTP, 2007; IARC, 2012).

In goats and heifers, the mean residence time (mean time the chemical remained in the body) was five hours following oral and intravenous (i.v.) exposure. Distribution was primarily to the liver, kidneys and lungs. The identified metabolites were 5-methyl hydantoin, 2-methylhydantoic acid and urea. The chemical and its metabolites were mainly excreted in the urine, but were also identified in the milk of pregnant and postpartum cows (NTP, 2007; IARC, 2012).

The chemical forms complexes with enzymes such as the cytochrome P450 (CYP), and is reported to significantly inhibit CYP2E1 activity in rat liver, and CYP2C9 activity in human and rat microsomes (IARC, 2012).

Acute Toxicity

Oral

The available information indicates that the chemical has moderate acute oral toxicity in animals and hazard classification is warranted.

The median lethal dose (LD50) is 751 mg/kg bw in rats, 370 mg/kg bw in mice, and 590 mg/kg bw in chickens (NTP, 2007; HSDB).

The chemical is associated with acute convulsant activity. In mice, acute neurological effects including tremor, restlessness, sialorrhoea (excessive drooling), opisthotonus (spasm of the back muscles) and tonic extensor seizure at high doses, and balance disorders at lower doses were observed. An oral convulsant dose (CD50) of 360 mg/kg bw was determined for mice. Rabbits and one day old chicks also showed convulsions (dose not reported) (NTP, 2007).

The chemical is a toxic by-product of fermentation in ammoniated hay forage for livestock. Acute effects (neurological signs and convulsant activity) were reported in animals fed with commercially ammoniated food. Facial twitching, body tremors followed by opisthotonus and convulsions were observed in ewes fed with ammoniated hay. Sheep, and calves that were nursed by cows fed ammoniated hay showed neurological signs including febrile seizure (caused by a fever), hyperexcitement, abnormal circling behaviour and epileptoid seizures (NTP, 2007).

Young Holstein calves orally administered the chemical up to a dose of 400 mg/kg bw showed similar signs to those nursed by dams that consumed ammoniated hay. Mortality occurred within three hours following administration at 400 mg/kg bw, and within 3–8 hours at 200 mg/kg bw. No effects were observed at =50 mg/kg bw (HSDB).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Corrosivity

The chemical is reported to be irritating and corrosive to the skin of animals. It is also reported to be irritating to rabbit eyes, according to a Draize test (HSDB). No irritation scores are available for animal studies; however, based on similar effects reported in humans, hazard classification is warranted.

In humans, the chemical is reported to be irritating, and causes burns on the skin and eyes. It is also reported to be 'extremely destructive to the tissue of the mucous membranes and upper respiratory tract' (HSDB).

Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not harmful up to 100 mg/kg bw/day. The effects are not sufficient to warrant hazard classification.

The liver in rats and the lungs in female mice were observed to be the target organs for chemical-induced toxicity. Female rats displayed neurological effects at ≥5000 ppm (300 mg/kg bw/day) in 14-week studies, possibly due to metabolism and renal saturation (see **Toxicokinetics**). The chemical did not induce consistent thyroid hormone effects (triiodothyronine T3, thyroxine T4 and thyroid stimulating hormone TSH) in both rats and mice in 14-week studies (NTP, 2004; NTP, 2007).

In a repeated dose toxicity study (OECD TG 408), Fischer 344 (F344) rats (n = 10/sex/dose) were administered the chemical in the diet at 0, 625, 1250, 2500, 5000 or 10000 ppm (equivalent to 0, 40, 80 160, 300 and 560 mg/kg bw/day), daily for 14 weeks. Significantly reduced mean body weight gains were observed at ≥2500 ppm, and reduced food consumption at ≥5000 ppm. Clinical findings at ≥2500 ppm included nasal or eye discharge, ruffled fur, abnormal breathing and ataxia. Neurobehavioural abnormalities were observed at doses ≥5000 ppm on days 29 and 82, and included increased respiration and mild tremors, tiptoeing, hunched posture, piloerection, coordination impairment, ataxia and pupillary constriction. Transient erythrocytosis, and microcytic, normochromic, nonresponsive anaemia was observed at ≥2500 ppm. Dose-dependent increases in relative weights were observed in the kidney and liver of males, and the liver of females, at ≥2500 ppm. Increased incidences of cytoplasmic hepatocyte vacuolisation were found in the liver of males at ≥2500 ppm and in females at ≥10000 ppm. Effects on the reproductive organs in males were testes degeneration at ≥5000 ppm, and atrophy and inflammation of the prostate, and hypospermia of the epididymis at 10000 ppm. A no observed adverse effect level (NOAEL) of 1250 ppm (80 mg/kg bw/day) was established based on hepatic effects at 2500 ppm (NTP, 2004; HSDB).

In another 14-week repeated dose toxicity study, B6C3F1 mice (n = 10/sex/dose) were administered the chemical in the diet at the same doses as in the 14-week rat study (equivalent to 0, 100, 240, 440, 915, or 1840 mg/kg bw/day in males and 0, 110, 240, 540, 1130 or 3180 mg/kg bw/day in females). At the highest dose, mortality occurred in 1/10 males (week 4) and 7/10 females (weeks 1 and 2). Significantly reduced mean body weight gains were observed at ≥1250 ppm for males and in all females. Minimal, nonresponsive anaemia was observed in all exposed females. Decreased absolute liver weight at the highest dose for males, and increased relative liver weights in all exposed groups were reported. Female mice showed significant changes (decreased absolute and increased relative weights) in the heart, right kidney, and liver at ≥2500 ppm (540 mg/kg bw/day). No significant differences were observed in reproductive organ parameters (sperm motility and vaginal cytology). No tissue lesions were related to exposure to the chemical. The NOAEL was determined as 10000 ppm (1840–3180 mg/kg bw/day) (NTP, 2004).

In 15-day oral studies, rats and mice (n = 5/sex/dose) were administered the chemical at 0, 300, 800 or 2500 ppm (equivalent to 0, 30, 80, or 220 mg/kg bw/day (rats), and 0, 65, 170, or 500 mg/kg bw/day (mice)). No mortality, and no significant differences in mean body weight, exposure-related clinical findings or gross or microscopic lesions were observed (NTP, 2004).

In two-year chronic oral studies, F344 rats (n = 60/sex) were exposed to the chemical at 0, 625, 1250, or 2500 ppm (males), or 0, 1250, 2500 or 5000 ppm (females), and B6C3F1 mice at 0, 312, 625, or 1250 ppm. Decreased mean body weights (two highest doses for rats and mice) and decreased food consumption (high dose female rats) were observed. Female rats showed neurological effects (clonic seizures, excitability, hyperactivity and impaired gait) at ≥2500 ppm (120 mg/kg bw/day), and all exposed rats displayed significantly increased incidences of liver lesions (hepatic histiocytosis, chronic inflammation and focal fatty changes). In mice, significantly increased alveolar epithelium hyperplasia was observed for female mice at 1250 ppm (170 mg/kg bw/day), and was considered to be a precursor to lung neoplasms (see **Carcinogenicity**) (NTP, 2007).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

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

The chemical gave negative results in bacterial reverse mutation assays with several strains of *Salmonella typhimurium* at concentrations up to 10000 µg/plate, with or without metabolic activation (NTP, 2007).

The chemical gave negative results in three in vivo assays (NTP, 2007). There were no increases in frequencies of micronucleated polychromatic erythrocytes (PCEs) in the bone marrow cells of male rats or male mice, administered the chemical intraperitoneally (i.p.) up to 100 mg/kg bw; or in the peripheral blood of mice administered the chemical in the diet at doses up to 10000 mg/kg bw/day for 14 weeks. The percentage of polychromatic erythrocytes (PCEs) (among total erythrocyte population) declined with increasing dose and was significantly depressed at the highest dose in the bone marrow of male rats (NTP, 2007).

Carcinogenicity

Based on the available data, the chemical is considered to have carcinogenic activity in animals, warranting hazard classification.

The International Agency for Research on Cancer (IARC) has classified the chemical as '*possibly carcinogenic to humans*' (Group 2B), based on sufficient evidence in experimental animals (IARC, 2012).

In a two-year carcinogenicity study, B6C3F1 mice (n = 50/sex/dose) were administered the chemical in the diet at 0, 312, 625 or 1250 ppm (equivalent to 0, 40, 80 or 170 mg/kg bw/day). Significantly increased incidences (dose/concentration related) of alveolar/bronchiolar adenoma or carcinoma were observed in males at 1250 ppm, and in females at ≥625 ppm. Incidences of carcinoma at the highest dose exceeded the historical control ranges. As the chemical did not cause effects in the respiratory epithelium of mice in 14-week repeated dose studies (see **Repeat dose toxicity**) at a dose up to 10000 ppm (3180 mg/kg bw/day), the mode of action for lung tumours in mice has yet to be elucidated (NTP, 2007; IARC, 2012).

In another two-year carcinogenicity study, F344 rats (n = 50/sex) were administered the chemical in the diet at 0, 625, 1250 or 2500 ppm for males, and 0, 1250, 2500 or 5000 ppm for females (equivalent to 30, 55 or 115, and 60, 120 or 260 mg/kg bw/day, respectively). At the highest dose, significantly higher incidences (compared with controls) of mononuclear cell leukaemia were observed in females, and exceeded historical controls. It is stated that although this particular leukaemia is common in F344 rats, exposure to the chemical may have quickened the process. There were lower incidences of pituitary gland adenoma, combined phaeochromocytoma of the adrenal gland in males, and pituitary gland and clitoral gland adenoma, mammary gland fibroadenoma and uterine stromal polyps in females (NTP, 2007; IARC, 2012). The IARC stated that the lower incidences 'could not be attributed to loss of body weight alone' (IARC, 2012).

Reproductive and Developmental Toxicity

No specific reproductive or developmental studies are available for the chemical. Based on the testicular degenerative effects observed in male rats at doses ≥300 mg/kg bw/day in the 14-week repeated dose oral toxicity study, the chemical is considered to have some potential to cause reproductive toxicity in male rats. However, the available information is not sufficient to warrant hazard classification.

A 14-week repeat dose toxicity studies in rats showed effects on male reproductive organs, including degeneration of seminiferous tubules of the testes and decreased reproductive organ weights at ≥5000 ppm (300 mg/kg bw/day), atrophy of the prostate gland, and decreased epididymal sperm motility at 10000 ppm (560 mg/kg bw/day) (see **Repeat Dose Toxicity**). Decreased testes weights could be associated with reduced body weights. However, no instances of testicular degeneration resulting from reduced body weight alone were identified. Based on concentration-dependent testicular degeneration effects, the NTP concluded that the chemical is a reproductive toxicant in male rats (NTP, 2007).

In another study, the chemical injected subcutaneously as a single dose to male SD rats at doses of 50–100 mg/kg bw caused decreased lutinising hormone secretion, testosterone secretion and dose-dependent formation of testicular interstitial fluid. Male fertility was inhibited, thus suggesting a disruption of pituitary luteinising hormone secretion regulatory mechanisms (NTP, 2004; NTP, 2007).

The chemical is listed on the US EPA's Universe of Chemicals list for potential endocrine disruptor screening and testing (US EPA, 2012).

Other Health Effects

Neurotoxicity

Acute and repeated dose toxicity studies in animals have reported neurological symptoms including tremor, restlessness, excessive drooling, opisthotonus, balance disorders, facial twitching, seizure, hyperexcitement, and abnormal circling behaviour (see **Acute** and **Repeat Dose Toxicity**).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects (irritation/corrosion);
- systemic acute effects (acute toxicity from oral exposure); and
- systemic long-term effects (carcinogenicity).

Public Risk Characterisation

The chemical has potential domestic use in oven cleaners (NTP, 2007). However, the US Household Products Database does not indicate any domestic use of the chemical. Currently, there are no restrictions in Australia on using this chemical in domestic products. In the absence of any regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk if used in domestically available oven cleaners.

Occupational Risk Characterisation

During product formulation, oral, 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.

Given the critical local, systemic acute and long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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 hazard classification of the chemical (refer to **Recommendation** section).

NICNAS Recommendation

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.

If any information becomes available to indicate significant consumer exposure to the chemical in oven cleaners in Australia, risks to public health and safety may need to be managed by changes to poisons scheduling.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1B (H314)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)	May cause cancer - Cat. 1B (H350)

[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, dermal, ocular and 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;
- 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[s] 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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