Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

1H-Imidazole, 1-methyl-

Evaluation statement

14 January 2022

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AICIS evaluation statement

Subject of the evaluation

1H-Imidazole, 1-methyl-

Chemical in this evaluation

Name	CAS number
1H-Imidazole, 1-methyl-	616-47-7

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).This evaluation is a human health risk assessment for all identified industrial uses of the chemical.

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of the chemical in Australia.

Based on overseas use information, the chemical has reported domestic uses including in machine wash liquids/detergents, automotive care products, paints, lacquers, coatings, adhesives, binding agents and air fresheners. The chemical has reported commercial uses including in reprographic agents, insulating materials, surface active agents, and non-agricultural pesticides and preservatives. The chemical has reported site limited uses including in oil and gas exploration, polymers, pH regulators and process regulators, and in the manufacture of other chemicals and materials.

Human health

Summary of health hazards

The critical health effects for risk characterisation include acute oral and dermal toxicity, and skin and eye corrosive effects. Systemic health effects following repeated exposure cannot be ruled out. No data are available to evaluate skin sensitisation and carcinogenicity endpoints for the chemical.

The chemical has moderate acute oral toxicity with a median lethal dose (LD50) of 1144 mg/kg body weight (bw) in rats. The chemical has moderate acute dermal toxicity with a LD50 of 400–640 mg/kg bw in rabbits.

The chemical is corrosive to the skin and eyes. Necrosis, erythema and oedema were observed within 5 minutes of exposure of the skin in Vienna white rabbits and scoring at 8 days was not possible. The corrosive effects were irreversible. Eye effects following exposure to the chemical included cauterisation of the mucous membrane. Maximum scores for corneal opacity, conjunctivae and chemosis were 4, 3 and 4, respectively. The effects on the eye of rabbits were not fully reversible during the observation period of 8 days.

Based on the available data, systemic health effects following repeated exposure to the chemical cannot be ruled out. In two 14 day dose ranging studies, Wistar rats showed body weight loss and increased cholesterol and urea levels at dose level of 90 mg/kg bw/day, and severe effects on body weight and food consumption at dose levels of 125 mg/kg bw/day and 250 mg/kg bw/day. In a repeated oral toxicity study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 408, Wistar rats (10/sex/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day for 91 days (males) or 92 days (females). The reported no observed adverse effect level (NOAEL) was 90 mg/kg bw/day for both sexes, based on no signs of systemic toxicity up to the highest dose level tested. In a combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD TG 422, Wistar rats (10/sex/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day. The NOAEL for both sexes was 30 mg/kg bw/day based on changes to urea, cholesterol, chloride and phosphate levels, and urinalysis findings.

Based on the available data, the chemical is not considered to have genotoxic potential. The chemical was negative in a bacterial reverse mutation assay and two in vitro mammalian cell assays using Chinese hamster ovary (CHO) cells and Chinese hamster lung fibroblasts (V79), respectively.

Based on the available data, the chemical is not expected to cause specific adverse effects on fertility and development. In a combined repeated dose toxicity study with reproductive and developmental toxicity screening test according to OECD TG 422, Wistar rats (10/sex/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day. The reported NOAEL for reproductive and developmental effects was 90 mg/kg bw/day (the highest dose tested). In a prenatal developmental toxicity study conducted according to OECD TG 414, female Wistar rats (25/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day from gestation days (GD) 6–19. The reported NOAEL for maternal and developmental effects was 90 mg/kg bw/day (the highest dose tested).

Health hazard classification

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Acute toxicity – dermal	Acute Tox. 3	H311: Toxic in contact with skin
Skin corrosion	Skin Corr. 1B	H314: Causes severe skin burns and eye damage

Summary of health risk

Public

No information is available on the uses of the chemical in Australia. Based on overseas use data, the chemical has domestic uses including in machine wash liquids/detergents, paints, adhesives and air fresheners. The main route of public exposure to the chemical is expected to be dermal and incidental ocular exposure during use of the domestic products. However, exposure to the chemical is expected to be minimal and of short duration. The chemical in domestic products is likely to be at low concentrations which would not result in corrosive effects or acute toxicity.

Workers

During product formulation and manufacture, 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, cleaning and maintenance of 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 may vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical local effects and systemic health effects following acute exposure, the chemical could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (refer to the **Recommendations** section). Control measures implemented due to the corrosivity classification are expected to be sufficient to protect workers from any potential repeated dose effects.

Conclusions

The conclusions of this evaluation are based on the information described in this statement. Obligations to report additional information about hazards under section 100 of the Industrial Chemicals Act 2019 apply.

The Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory. The proposed means of managing the risks identified during this evaluation are set out in the **Recommendations** section.

Recommendations

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include the classifications relevant to work health and safety.

Information on managing identified risks

The information in this report, including recommended hazard classifications, should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an

employer) to determine the appropriate controls under the Model Work Health and Safety Regulations.

Control measures that could be implemented to manage the risk arising from oral, dermal, ocular and inhalation exposure to the chemical 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
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- regularly cleaning equipment and work areas
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

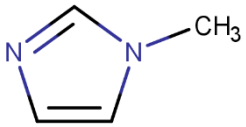
Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

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.

Model codes of practice, available from the SWA website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Supporting information

Chemical identity

Chemical name	1H-Imidazole, 1-methyl-
CAS No.	616-47-7
Synonyms	1-methylimidazole *N*-methylimidazole
Structural formula	
Molecular formula	C4H6N2
Molecular weight (g/mol)	82.10
SMILES	N=1C=CN(C1)C
Chemical description	-

Relevant physical and chemical properties

Physical form	Colourless liquid at 20°C and 1013 hPa
Melting point	-6°C
Boiling point	198.9 °C
Vapour pressure	0.351 hPa at 20°C
Water solubility	1000 g/L at 20°C
pKa	7.01 ± 0.10 at 25°C

Introduction and use

Australia

No information is available on the introduction and use of this chemical in Australia.

International

The chemical has reported potential domestic uses including in (REACH):

- machine wash liquids/detergents
- automotive care products
- paints, lacquers and coatings
- adhesives and binding agents
- air fresheners.

The chemical has reported commercial uses including in (SPIN):

- reprographic agents
- insulating materials
- surface active agents
- non-agricultural preservatives.

The chemical has reported site limited uses including in (REACH; SPIN):

- oil and gas exploration
- polymers
- pH regulators
- process regulators
- viscosity adjustors
- water treatment products
- construction materials.

The chemical has reported uses in the manufacture of (REACH; SPIN):

- chemicals
- rubber and plastic products
- fabricated metal products
- antifoaming agents
- furniture
- transport equipment
- electrical equipment.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is classified as hazardous with the following risk phrases for human health in the HCIS (SWA):

- Acute oral toxicity – Category 4: H302 (Harmful if swallowed)
- Acute dermal toxicity – Category 4: H312 (Harmful in contact with skin)

- Skin corrosion – Category 1B: H314 (Causes severe skin burns and eye damage).

No specific exposure standards are available in Australia (SWA).

International regulatory status

Exposure standards

The following exposure standards are identified:

- protective action criteria (PAC) 1, 2 and 3 of 2.3, 25 and 150 mg/m^3, respectively, in the U.S. (Department of Energy).

Health hazard information

Toxicokinetics

The chemical has a log Kow value between -1 and 4, which favours absorption by passive diffusion. Furthermore, the molecular weight just below 200 g/mol makes the chemical favourable for adsorption. Overall, this suggests that 1-methylimidazole may be readily absorbed dermally and by the gastrointestinal and respiratory tracts (REACH).

Acute toxicity

Oral

Based on the available data, the chemical has moderate acute oral toxicity, which warrants hazard classification (refer to **Health hazard classification** section).

In an acute oral toxicity study not compliant with good laboratory practice (GLP), US rats (5/sex/dose) were administered the chemical (in water) by oral gavage at doses of 200, 400, 800, 1000, 1250 or 1600 µL/kg bw. The mortalities reported at doses of 800, 1000, 1250 and 1600 µL/kg bw were 2/10, 7/10, 5/10 and 10/10 animals, respectively. The only clinical sign reported was tonic cramps. The median lethal dose (LD50) reported was 1100 µL/kg bw (approximately 1144 mg/kg bw) in rats (REACH).

The chemical is classified as hazardous in the HCIS (SWA) as Acute Toxicity (Oral) – Category 4. The available data are consistent with this classification.

Dermal

Based on the available data, the chemical has moderate acute dermal toxicity. The available data warrant an amendment to the hazard classification (refer to **Health hazard classification** section).

In a non-GLP compliant acute dermal toxicity study, the chemical was applied to the skin (under occlusion) of Vienna white rabbits (3/sex for 250 and 640 mg/kg bw; 6/sex for 400 mg/kg bw) without controls. The mortalities reported were 2/6 males at 400 mg/kg bw and 1/3 males and 3/3 females at 640 mg/kg bw. The reported clinical signs included apathy, accelerated breathing, spasms, salivation, excess lacrimation and narrowed pupils. Local irritation of the skin including erythema, necrosis and persistent oedema were observed.

Gross pathological findings included dilatation of the heart and hyperaemia in the lungs in animals that died during the study. The reported LD50 was 400–640 mg/kg bw in rabbits (REACH).

The chemical is classified as hazardous in the HCIS (SWA) as Acute Toxicity (Dermal) – Category 4. The available data are not consistent with this classification and warrant Acute Toxicity (Dermal) – Category 3.

Inhalation

Limited data are available for this chemical. Based on the available data, the chemical has low acute inhalation toxicity.

In a non-GLP compliant acute inhalation toxicity study with limited details reported, rats (3/sex; strain unspecified) were exposed to the chemical as a saturated vapour (type of inhalation unspecified) for 8 hours. Due to the low vapour pressure, the technically highest attainable concentration was approximately 1.2 mg/L when the test substance was evaporated at 20°C (concentration not determined), which is below cut off values for limit testing. The reported clinical signs included signs of escape behaviour and distinct irritation of mucous membranes. No mortalities occurred during the study (REACH).

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is considered to be corrosive to the skin.

In a non-GLP compliant acute dermal irritation study, the chemical (without vehicle) was applied to the skin (area of exposure: 2.5 x 2.5 cm; under occlusion) of Vienna white rabbits (n = 2; sex unspecified) for 1, 5, 15 minutes and 20 hours and observed for 8 days. After the exposure time had elapsed, the skin was washed with Lutrol (50%). At the 24 hour observation, the treatment caused scaling (after 1 min exposure), necrosis and hardening of the skin (after 5 min exposure), severe necrosis (after 15 min exposure), and severe necrosis and scarring of the skin (after 20 h exposure). Erythema and oedema scores ranging from 2–3 were reported at the 24 hour observation and scoring at 8 days was not possible. The corrosive effects were irreversible. The chemical was considered corrosive to the skin under the conditions of the study (REACH).

The chemical is classified as hazardous in the HCIS (SWA) as Skin corrosion – Category 1B. The available data are consistent with this classification.

Eye irritation

Based on the available data, the chemical causes serious eye damage.

In a non-GLP compliant eye irritation study, the chemical (0.05 mL; without vehicle) was applied to 1 eye, while the other eye served as a control, of Vienna white rabbits (n = 2; sex unspecified) and observed 1 hour, 24 hours and 8 days after instillation. Maximum scores for corneal opacity, conjunctivae and chemosis were 4, 3 and 4, respectively. The effects were not fully reversible within 8 days. Cauterisation of the mucous membrane was observed at every time point. The chemical was considered corrosive to the eyes under the conditions of the study (REACH).

The chemical is classified as hazardous in the HCIS (SWA) as Skin corrosion – Category 1B and the hazard statement, 'Causes severe skin burns and eye damage' (H314). As a skin corrosive chemical, 1H-Imidazole, 1-methyl- also has the ability to cause eye damage. This classification is appropriate for eye damage effects.

Sensitisation

No data are available to evaluate this hazard endpoint.

Repeat dose toxicity

Oral

Based on the available data, systemic health effects following repeated exposure to the chemical cannot be ruled out.

In a dose range study, Wistar rats (3/sex/dose) were administered the chemical (in 1% carboxymethylcellulose aq.) by oral gavage at doses of 0, 60, 125 or 250 mg/kg bw/day for 14 days. Severe effects on body weight and food consumption were observed in the mid and high dose groups at study day 3 (= day 4 of administration) and for both sexes (more prominent in males than in females). Thus, the doses were reduced from 125 to 15 mg/kg bw/day and from 250 to 30 mg/kg bw/day, respectively, as from study day 4. The body weights remained slightly reduced until the end of the study (REACH).

In another dose range study, Wistar rats (4/sex/dose) were administered the chemical (in 1 % carboxymethylcellulose aq.) by oral gavage at doses of 0 or 90 mg/kg bw/day for 14 days. Females dosed with the test substance showed piloerection of the fur on several study days and food consumption was statistically significantly decreased (-41.5% for males and -26.8% for females) on study day 3, but recovered afterwards. Increased cholesterol levels were observed in males and females dosed with the test substance, indicating systemic toxicity. Males were more susceptible to the test substance, and their body weight gain was statistically significantly reduced (-11.6 g) on study day 3 and their urea levels were increased on study day 14 (REACH).

In a repeated oral toxicity study conducted according to OECD TG 408, Wistar rats (10/sex/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day for 91 days (males) or 92 days (females). No mortalities or clinical signs of toxicity were reported, except for salivation and ploughing nose-first into bedding observed in the 90 mg/kg bw/day (high) dose group. Both were considered by the study authors to be a result of upper digestive tract local irritation after administration of the corrosive test substance.

No test substance related changes of mean body weights and mean body weight change values in both sexes were observed. In males of the high dose group, body weight and body weight change were significantly decreased on study day 7. No test substance related findings were observed in food or water consumption.

The following treatment related findings were considered by the study authors to be adaptive rather than adverse effects:

- In males of the high dose group, relative reticulocyte counts and urea values were higher compared to controls and slightly above the historical control range.

- In males of the high dose group, the urine volume was decreased and considered as maybe treatment-related.
- In females of the high dose group, chloride levels were decreased and the values were marginally below the historical control range.

There was a statistically significant increase in the relative liver weights of males in the mid (105%) and high dose (113%) groups, and in females of the high dose group (110%). Histopathological examination of the liver revealed minimal to slight centrilobular hypertrophy in males of all dose groups, and in females of the mid and high dose groups without correlated changes in clinical chemistry parameters for liver function. The reported NOAEL was 90 mg/kg bw/day for both sexes, based on no signs of systemic toxicity up to the highest dose level tested (REACH).

In a combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD TG 422, Wistar rats (10/sex/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day. The duration of treatment covered a 2 week premating and a mating period in both sexes, approximately 2 days post mating in males, and the entire gestation period as well as approximately 2 weeks of lactation period (males: up to 28 days, females: up to 55 days) (REACH).

Parental animals:

No mortalities or clinical signs of toxicity were reported. Several animals (both sexes) in the high dose group exhibited salivation for a few minutes immediately after administration which was likely to be induced by the unpleasant taste or local irritation.

The mean body weights of the male and female animals in all test substance treated groups were comparable to the control group during the study period. Males in the high dose group had significantly lower body weight change (-37% compared to control) during premating days 0–7. Females in the high dose group had significantly lower body weight change (-65% compared to control) during postnatal days 0–4. Food consumption of the high-dose males was statistically significantly below controls during premating days 0–7 (-11%).

In both sexes in the high dose group, the absolute and relative weights of the liver were significantly increased. Histopathological examination of the liver revealed centrilobular hypertrophy which was consistent with the liver weight increase observed. In males of the high dose group, urea, cholesterol and inorganic phosphate levels were increased, while chloride concentrations were decreased. In addition, more phosphate crystals and transitional epithelial cells were observed in the urine sediment in males in the high dose group. In females of the high dose group, urea levels were higher. The reported NOAEL was 30 mg/kg bw/day for both sexes based on changes to urea, cholesterol, chloride and phosphate levels, and urinalysis findings (REACH).

Genotoxicity

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

In vitro

- In a bacterial reverse mutation test conducted according to OECD TG 471, the chemical was negative in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535

and TA 1537 at concentrations up to 5000 µg/plate with and without metabolic activation (REACH).
- In a mammalian cell gene mutation test conducted in Chinese hamster ovary (CHO) cells according to OECD TG 476, the chemical did not cause any relevant increase in the mutant frequencies up to 850 µg/mL in the presence or absence of metabolic activation (REACH).
- In a mammalian cell micronucleus test conducted in Chinese hamster lung fibroblasts (V79) according to OECD TG 487, the chemical did not cause any biologically relevant increase in the number of cells containing micronuclei up to 850 µg/mL in the presence or absence of metabolic activation (REACH).

Carcinogenicity

No data are available to evaluate this hazard endpoint.

Reproductive and development toxicity

Based on the available data, the chemical is not expected to cause specific adverse effects on fertility or development following oral exposure.

In a combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD TG 422, Wistar rats (10/sex/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day (refer to **Repeat Dose Toxicity** section). No effects were observed in the parental mating and fertility indices, mean gestation duration, implantation number, mean number of pups per dam, and live birth indices in any of the dose groups. No effects on pup body weights or pathology at necropsy were observed. The NOAEL for reproductive and developmental toxicity was 90 mg/kg bw/day (the highest dose tested) (REACH).

In a prenatal developmental toxicity study conducted according to OECD TG 414, female Wistar rats (25/dose) were administered the chemical (in water) by oral gavage at doses of 0, 10, 30 or 90 mg/kg bw/day from GD 6–19. On GD 20, all surviving dams were sacrificed and examined macroscopically (REACH).

No substance related or spontaneous mortalities in any of the groups were reported. Three females in the high dose group salivated within the 2 hour examination interval on GD 17–19. Only pregnant dams were used for calculations of mean water consumption, food consumption, body weight and body weight change (2 female rats from the high dose group were excluded from such calculations as they were not pregnant). The mean food consumption of the mid and high dose groups was significantly reduced (-10% and -26 % below control, respectively) from GD 6–10, but recovered afterwards. Consistent with the reduced food consumption, the body weight changes of the mid and high dose groups were significantly reduced on GD 6–8. However, average body weight change values of these test groups were quite similar to the control value for the entire treatment period (GD 6–19).

There were no test substance related and/or biologically relevant effects on the values calculated for the post implantation losses, the number of resorptions and viable foetuses. No test substance related necropsy findings were observed in any dam.

There were no biologically relevant effects on the mean placental weights, the mean foetal weights, foetal external malformations or foetal external variations.

Three soft tissue variations (short innominate, dilated renal pelvis and dilated ureter) were detected in foetuses. The incidence of dilated renal pelvis in the foetuses were statistically significantly increased in the low and high dose groups, and consequently the total incidence of foetal soft tissue variations was also increased in these groups. The findings were considered as incidental as they were not dose related and within the historical control data.

A number of skeletal malformations were detected in foetuses of all test groups and controls affecting the skull, vertebral column, sternum and humerus, with each foetus in the low and high dose and control group being associated with external findings. The findings were not considered to be test substance related as all findings were single cases and most of them were within the historical control data. Skeletal variations of different bone structures were observed in all test groups, with or without effects on corresponding cartilages. The observed skeletal variations were related to several parts of the foetal skeleton and appeared without any dose relationship and were within historical control data. Some isolated, non-dose related cartilage findings without an impact on the respective bone structures of the skull, vertebral column, sternum and ribs, occurred in all test groups. The NOAELs for maternal and developmental toxicity were 90 mg/kg bw/day (the highest dose tested), based on no evidence of maternal or developmental toxicity (REACH).

References

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SPIN (Substances in Preparation in Nordic Countries) (n.d.) *SPIN Database,* SPIN website, accessed October 2021.

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