Hydrazine, 1,1-dimethyl-: Human health tier II assessment

27 November 2014

CAS Number: 57-14-7

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.

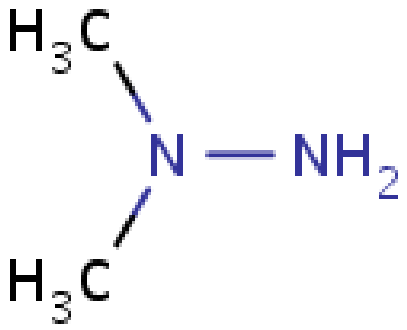
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	dimazine 1,1-dimethylhydrazine N,N-dimethylhydrazine hydrazine, N,N-dimethyl- unsymmetrical dimethylhydrazine (UDMH)
Structural Formula	
Molecular Formula	C2H8N2
Molecular Weight (g/mol)	60.09
Appearance and Odour (where available)	Colorless liquid with characteristic ammonia like fishy odor
SMILES	CN(C)N

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 European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; Galleria Chemica; the International Agency for Research on Cancer (IARC); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported commercial use (IARC):

- as a stabiliser for organic peroxide fuel additives;
- an an absorbent for acid gases; and

- in photography.

The chemical has reported mostly site-limited use:

- primarily as a component of jet fuel; and
- as a chemical intermediate.

The chemical has also reported non-industrial use as a plant growth regulator.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed under the entry 'Hydrazine (302-01-2), its derivatives and their salts' in the EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products (Galleria Chemica; CosIng).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- T; R23/25 (acute toxicity)
- C; R34 (corrosivity)
- Carc. Cat. 2; R45 (carcinogenicity)

Exposure Standards

Australian

The chemical has an exposure standard of 0.025 mg/m^3 (0.01 ppm) time weighted average (TWA).

International

The following exposure standards are available (Galleria Chemica):

- 0.02–0.025 mg/m^3 (0.01 ppm) TWA in Canada, Denmark, Indonesia, Ireland, Norway, Spain and California
- 0.2–0.25 mg/m^3 (0.1 ppm) TWA in Estonia, France, Iceland and Malaysia
- 0.5 mg/m^3 (1 ppm) TWA in Quebec, Greece, Mexico, the USA (except California) and Singapore

Health Hazard Information

The chemical has been reported to potentially share a common mechanism of action with the related compound hydrazine (CAS No. 302-01-2), involving a direct binding of the free amino group to cellular molecules. Both hydrazine and the chemical can form hydrazones with vitamin B6 derivatives in the body, leading to a deficiency in vitamin B6, and causing convulsions, dermatitis and anaemia. For both hydrazine and the chemical, the primary target organ is reported to be the central nervous system (CNS) regardless of the route of exposure (ATSDR, 1997).

Therefore, when the toxicity data for the chemical are not available or insufficient to derive hazard properties, data on hydrazine are considered relevant to use to determine likely systemic toxicity effects.

Toxicokinetics

In rats, rabbits, cats, dogs and monkeys, the radiolabelled chemical was rapidly absorbed into the blood regardless of the route of administration. The chemical was rapidly excreted via the kidneys; 30–50 % of the administered dose was excreted in its unchanged form in the urine within five hours in cats and dogs. The chemical had no preferential target for accumulation in the body. At doses below 10 mg/kg bw, the chemical was not detectable in the blood (Back et al., 1963, cited in HSDB).

The chemical, specified as unsymmetrical dimethylhydrazine (UDMH), was almost completely absorbed when applied subcutaneously (HSDB). It was absorbed rapidly from the skin into the blood. Dogs exposed to a single dermal dose of the chemical at 300–1800 mg/kg bw had a maximum blood level of 130 µg/mL, three hours after application (ASTDR, 1997).

The radiolabelled chemical injected intraperitoneally (i.p.) to Sprague Dawley (SD) rats was excreted primarily in the urine (53–70 % radioactivity) and in expired air as CO_2 (12–21 %), while 11–35 % remained in the tissues (Dost et al., 1964).

It is reported that while the metabolic pathways of hydrazine and the chemical 'are similar in some ways, there are some important differences' (ATSDR, 1997). The chemical was shown to undergo N-demethylation in vivo given the presence of hydrazones in the urine of rats, while hydrazine is reported to undergo acetylation. At least two independent enzymatic systems and one non-enzymatic pathway might be involved in the metabolism of the chemical. Both hydrazine and the chemical are reported to produce reactive intermediates such as methyl, acetyl and hydroxyl radicals (ATSDR, 1997).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia). The available data support this classification.

Acute toxicity data (details not available) indicate oral median lethal doses (LD50) of 122 mg/kg bw in the rat and 155 mg/kg bw in the mouse (ChemIDPlus; RTECS).

Dermal

The chemical has moderate acute dermal toxicity and warrants a hazard classification.

Acute toxicity data (details not available) indicate dermal LD50 values of 770 mg/kg bw in the rat, 1060 mg/kg bw in the rabbit and 1329 mg/kg bw in the guinea pig (ChemIDPlus; RTECS).

Single applications of the chemical to the skin of dogs (details not available) have been reported to induce opacity of the cornea and oedema, due to the chemical being translocated to the aqueous humour of the eye (HSDB).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic by inhalation' (T; R23) in HSIS (Safe Work Australia). The available rat data support this classification.

Acute toxicity data (study details not available) indicate the following median lethal concentrations (LC50):

- 252 ppm (0.618 mg vapour/L/4-hour) in the rat (ATSDR, 1997);
- 172 ppm (0.422 mg/L/4-hour) in the mouse, 392 ppm in the hamster (0.961 mg/L/4h) and 0.1 mg/L/4-hour in the guinea pig (ChemIDPlus; RTECS).

Observation in humans

Acute inhalation exposure to the chemical caused respiratory effects, nausea, vomiting, neurologic effects, pulmonary oedema and increased serum enzyme levels in humans (NRC, 2000).

Two workers exposed to a mixture of the chemical and hydrazine for approximately 90 minutes showed the following symptoms:

- one worker had a headache, nausea, weakness, tightness in the chest (indicative of pulmonary oedema), wet rales and rapid breathing, a sore throat and burning skin;

- the other had severe dyspnoea (shortness of breath) and developed pulmonary oedema.

Both workers recovered from these effects (NRC, 2000).

Two other individuals, who were exposed to an accidental spill of the chemical, experienced choking, difficulty in breathing and extreme nausea (NRC, 2000).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase 'Causes burns' (C; R34) in HSIS (Safe Work Australia). The available animal data indicate skin and eye irritation effects from exposure to the chemical. However, the concentrations of the chemical used in these studies have not been stated. The analogue compound, hydrazine, is a corrosive substance. Therefore, there is insufficient evidence to amend the existing hazard classification.

Application of small amounts of the chemical (concentration not stated) to the skin of rabbits or guinea pigs produced slight erythema (HSDB).

Single dermal applications of the chemical at 1200–1800 mg/kg bw to dogs produced serious systemic effects. However, only slight reddening of the skin was observed, indicating the chemical is 'at worst a mild skin irritant' (HSDB).

When the chemical was applied to the eyes of rabbits (concentration and duration of exposure not available) mild conjunctivitis and slight erythema, which cleared within five days, were observed. There was 'no permanent' damage to the rodent eye (HSDB).

A single application of the chemical (3 µL) to the eyes of rabbits produced conjunctivitis and erythema of the eyelid, but no corneal damage (ATSDR, 1997).

Observation in humans

Hydrazines vapours are 'highly irritating to the eyes, upper respiratory tract and skin' (HSDB).

Propellant hydrazines, such as the chemical were reported to induce pronounced skin irritation (HSDB).

Sensitisation

Skin Sensitisation

No data are available for the chemical.

However, the analogue compound hydrazine is classified as a skin sensitiser based on human data (NICNAS). There is a possibility of cross sensitisation to hydrazine and its salts (MAK, 2012).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

The absence of data is reported to be 'probably due to the corrosiveness of hydrazines and their ability to induce dermal sensitisation reactions' (ATSDR, 1997).

Inhalation

The studies available indicate some adverse health effects in animals. However, these studies have been conducted prior to the implementation of the OECD (Organisation for Economic and Cooperative Development) test guidelines. The purity of the test material used in these studies was not available.

Therefore, the data available are not sufficient to make a conclusion on the repeated dose inhalation toxicity of the chemical.

In a six-month inhalation study, dogs, rats and mice were exposed to the chemical at 0.05, 0.5 or 5 ppm for six hours/day, five days/week. Rats and mice were reported to exhibit fatty changes, angiectasis, hyaline degeneration of the gall bladder, and a congested liver, leading to a lowest observed adverse effect concentration (LOAEC) of 0.05 ppm (Haun et al., 1984, cited in ATSDR, 1997). However, the authors of the study reported that the only significant effect was transitory hepatotoxicity in dogs exposed to the chemical at 5 ppm (Haun et al., 1984).

Groups of rats and mice, both exposed to vapours of the chemical at 75 ppm (0.18 mg/L) for seven weeks or 140 ppm (0.343 mg/L) for six weeks (with exposure for six hours/day for five days/week), exhibited neurological and respiratory effects, and mortality at both doses (Rinehart et al., 1960, cited in HSDB).

Dogs intermittently exposed (five days/week, six hours/day) to the chemical vapour at 5 or 25 ppm for 13–26 weeks had neurotoxic effects such as lethargy, salivation, diarrhoea, ataxia, convulsions (see also **Neurotoxicity**) and haematological effects (mild anaemia with a 17–26 % decrease in the red blood cell count, haemoglobin and haematocrit at 5 ppm). Anaemia was more pronounced at 25 ppm after four weeks of exposure. Haemosiderosis of the spleen was noted at 5 ppm after 26 weeks, and the same effect was observed for Kupffer cells on the liver at 25 ppm after 13 weeks (Rinehart et al., 1960, cited in ATSDR, 1997). However, anaemic effects were not observed in other dog studies (exposed to the same concentrations of the chemical for a shorter duration) and therefore, ATSDR (1997) suggested that the impurities in the chemical might have contributed to the anaemic effects in the previous (Rinehart et al., 1960) study.

Genotoxicity

The chemical gave mixed results in both in vitro and in vivo assays. The analogue compound hydrazine is a Category 3 mutagen (NICNAS). Considering the range of positive in vivo data, a Category 3 hazard classification for mutagenicity is recommended for this chemical.

According to IARC (1999), there was 'conflicting evidence as to UDMH mutagenicity to bacteria'. In vitro tests on mammalian cells showed a potential for mutagenicity, with positive responses reported after metabolic activation (gene mutations in Chinese hamster lung V79 cells and in mouse lymphoma L5178Y cells; chromosomal aberrations in Chinese hamster ovary (CHO) cells and unscheduled DNA synthesis in mouse hepatocytes but not in rat hepatocytes).

In a few in vivo assays, the chemical caused somatic mutations in:

- *Drosophila melanogaster* at 150 mg/kg bw/day (IARC, 1999);
- separate studies in CD1 mice, in which parenteral administration (injection) of the chemical induced micronuclei in splenocytes (a single dose of 13.8 mg/kg bw/day), hepatocytes (two doses of 14 mg/kg bw/day) and spermatids (a single dose of 83 mg/kg bw/day) (IARC, 1999); and
- Swiss albino mice—DNA fragmentation in the lungs and liver was induced by the chemical injected (i.p.) five times at 42 mg/kg bw/day (Parodi et al., 1981, cited in IARC, 1999).

In a murine spermatogenesis test, B6C3F1 male mice were administered the chemical (single i.p. dose) at 10–70 % of the estimated LD50 of 125 mg/kg bw. Significantly decreased body weight, a clear increase in the percent of abnormally shaped sperm and reduced sperm production were observed. The chemical was cytotoxic to spermatogenic cells in mice (Wyrobek & London, 1973).

Other in vivo tests conducted with the chemical gave negative results for genotoxicity (Brusick & Matheson, 1976; IARC, 1999; HSDB):

- a micronucleus test in the bone marrow cells of mice (i.p. treated with single doses of 20, 83 or 500 mg/kg bw/day);
- an unscheduled DNA synthesis in kidney cells of Fischer 344 (F344) rats (i.p. injected with 50 mg/kg bw/day);
- a dominant lethal assay in mice (i.p. treated with 1 x 12.5 or 5 x 63 mg/kg bw/day);
- a sperm abnormality test on mice i.p. injected with 5 x 500 mg/kg bw/day;
- a host-mediated assay in mice orally given 140 mg/kg bw/day; and
- a sex-linked recessive lethal mutation assay in *D. melanogaster* injected with 1200 mg/kg bw/day.

Carcinogenicity

The chemical is classified as a Category 2 carcinogen with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Possibly carcinogenic to humans’ (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity based on animal testing (IARC, 1999). The chemical is a potent carcinogen, producing tumours primarily in the lungs of animals (ATSDR, 1997). More recently, the chemical has been identified as '*reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals' (NTP, 2011).

There are several studies indicating carcinogenic effects in animals with exposure to the chemical. Liver carcinomas were reported in 3/20 rats which were administered the chemical in drinking water for life at 70 mg/animal/day (IARC, 1974).

Swiss mice, which received the chemical in drinking water at 5 mg/day for 40 weeks, developed lung tumours (IARC, 1974). When groups of Swiss mice (n = 50/sex) were administered the chemical at 0.01 % in drinking water, angiosarcomas in various organs were seen in 79 % of animals, in addition to tumours in the lungs (71 %), kidneys (11 %) and the liver (6 %) (IARC, 1974).

Groups of 15 European hamsters treated with weekly subcutaneous injections of the chemical (37.3 and 32.5 mg/kg bw for males and females, respectively) for life developed peripheral nerve sheath tumours (neurofibrosarcoma, melanotic and unpigmented schwannoma) (IARC, 1999).

A six-month study in dogs, rats, mice and hamsters reported that inhaling the chemical at 5 ppm induced tumours only in rats and mice. The liver was the target organ with pre-neoplastic and neoplastic changes in both rats and mice, along with lesions in the lungs of rats (Haun et al., 1984).

Reproductive and Developmental Toxicity

Only limited data are available. Most of the studies available for the chemical do not use exposure routes relevant for human exposure (i.e. oral, dermal or inhalation). The analogue chemical hydrazine also has limited data and a hazard classification was not warranted (NICNAS). The information available is not sufficient to form a conclusion on the reproductive or developmental toxicity of the chemical.

Pregnant F344 rats exposed to the chemical (i.p. injections) at 30 or 60 mg/kg bw/day during gestation days 6–15 exhibited a significant decrease in maternal and foetus body weights, and a moderate increase in the number of malformations in foetuses (e.g. anophthalmia or severe microphthalmia, hydronephrosis, hydrocephalic foetus, unossified sternebrae) at 60 mg/kg bw, but not at 30 mg/kg bw. The study concluded that the chemical was not 'selectively embryotoxic or teratogenic in the rat' (Keller et al., 1984 cited in IARC, 1999).

Oral administration of the chemical at 200 mg/kg bw to mice induced a 71.3 % inhibition of thymidine incorporation into testicular DNA. However, the purpose of the study was to establish a link between known carcinogens and/or mutagens with DNA synthesis; consequently the observed effects could be due to the carcinogenic and/or mutagenic properties of the chemical (Seiler et al., 1977, cited in HSDB).

Other Health Effects

Neurotoxicity

The CNS was reported to be a major target for the chemical (ATSDR, 1997). Limited information indicates transient neurotoxic effects in humans and monkeys with exposure to the chemical. Nausea, headaches, vomiting and weakness were reported in two workers exposed to the chemical (see **Acute toxicity: Observation in humans**) (NCR, 2000; HSDB). A 31-year-old man exposed to the chemical reported 'neurological symptoms' that were easily treated (HSDB).

Monkeys injected with the chemical (doses not available) induced performance decrements that could last 6–9 hours. Doses above 30 mg/kg bw induced changes in learned behaviour (HSDB).

In a chronic study with mice, rats and cats exposed to the chemical by inhalation or i.p. injection, nervous tissue and the bronchopulmonary system were reported to be damaged (HSDB).

In inhalation studies, rats and mice exposed continuously to 75 ppm of the chemical occasionally exhibited tremors. In dogs exposed to the chemical intermittently at 25 ppm, depression, ataxia, salivation, emesis and seizures were observed after three days (Rinehart et al., 1960, cited in ATSDR, 1997).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects through oral, dermal or inhalation exposure; and
- systemic long-term effects (carcinogenicity and mutagenicity).

Inhalation exposure might also cause transient neurotoxic effects. Exposure to the chemical at high concentrations could cause corrosive or irritant effects.

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.

The National Toxicology Program (NTP) (2011) stated that the exposure to the chemical could be higher for people living near military installations that use the chemical as a propellant.

Occupational Risk Characterisation

During formulation or use of products containing this chemical, dermal, ocular and inhalation exposure of workers to the chemical might occur, particularly where manual or open processes are used. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemical could 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.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as in the table below.

This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Harmful in contact with skin (Xn; R21) Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Harmful in contact with skin - Cat. 4 (H312) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1B (H314)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
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 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 which may 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 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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Last update 27 November 2014

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