Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Carbamic acid, monoammonium salt (ammonium carbamate)

Evaluation statement

14 September 2021

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AICIS evaluation statement

Subject of the evaluation

Carbamic acid, monoammonium salt (ammonium carbamate)

Chemical in this evaluation

Name	CAS registry number
Carbamic acid, monoammonium salt	1111-78-0

Reason for the evaluation

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

Parameters of evaluation

A human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

No Australian use information are available. Based on international use information, the chemical is used as a buffering agent in cosmetics (e.g. hair colouring products) and domestic cleaning products. The whole chemical, or as a component of ammonium carbonate, may be added to the product. The species present will be dependent on pH and at neutral pH, the expected species are ammonium and bicarbonate.

The chemical also has reported commercial, site-limited, and non-industrial applications in food, biocides and pesticides.

Human health

Summary of health hazards

The critical health effects for risk characterisation include the potential for the chemical to cause serious eye damage. In a guideline eye irritation study, the chemical produced effects on the cornea that did not reverse in 21 days in one animal. The chemical was also predicted to cause irreversible damage to eyes in 2 ex vivo eye irritation studies.

Based on the available data (see supporting information), the chemical has moderate acute oral toxicity and may be irritating to the skin, particularly after prolonged exposure and may be irritating to nose, throat, respiratory tract and lungs at high levels of exposure.

The chemical:

- has low acute dermal toxicity
- is not a skin sensitiser
- is not considered to be genotoxic.

Based on information for metabolites, the chemical is not expected to be carcinogenic, toxic to reproduction and development, or cause systemic toxicity following repeated exposure.

Health hazard classification

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

Hazard class	Hazard category	Hazard statement
Acute toxicity – oral	Category 4	H302: Harmful if swallowed
Serious eye damage / eye irritation	Category 1	H318: Causes serious eye damage

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical

- by direct application of the chemical to the skin and/or hair
- by direct skin contact during use of domestic products
- by incidental skin and eye contact with the chemical during use
- by incidental inhalation from spray and loose powder cosmetic products.

The chemical is used as a buffering agent in cosmetics and; therefore, public exposure to the chemical under extreme pH conditions is not expected from cosmetic uses. Application of the chemical at current use and concentrations is not predicted to cause irritant and corrosive effects. Therefore, there are no identified risks to the public that require management.

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 higher concentrations is expected. The level and route of exposure will 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 systemic acute and local health effects, the chemical could pose a risk to workers. Control measures to minimise ocular and inhalation exposure are needed to manage the risk to workers (refer to the **Recommendation** section).

Conclusions

The conclusions of this evaluation are based on the information described in the 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 below.

Recommendations

Public health

Advice to industry

Ammonium carbamate (as a component of ammonium carbonate) may contain hazardous impurities, e.g. lead (up to 3 mg/kg) (CIR 2017).

Formulators of products containing the chemical should take into account the availability of hazardous impurities likely to be present in the products when determining label instructions in accordance with the Poisons Standard (the *Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP).

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include new classifications listed above.

Advice to industry

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.

Recommended control measures that could be implemented to manage the risk arising from 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
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

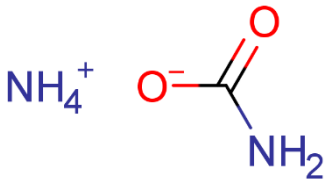
Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

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.

Model codes of practice, available from the Safe Work Australia 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	Carbamic acid, monoammonium salt
CAS number	1111-78-0
Synonyms	Ammonium carbamate; Carbamic acid, ammonium salt (1:1)
Structural formula	
Molecular formula	$CH_6N_2O_2$
Molecular weight (g/mol)	78.07
SMILES	C(N)(=O)[O-].[NH4+]
Chemical description	White crystalline powder with an ammonia-like odour

Introduction and use

Australia

No specific information on Australian use, import, or manufacturing has been identified for ammonium carbamate.

International

The following international uses of ammonium carbamate have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossier; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States Environmental Protection Agency's assessment for ammonium carbamate (US EPA 2006); and technical product information (BASF).

The chemical has reported cosmetic use as a buffering agent. Ammonium carbamate as a component of ammonium carbonate would be assumed to be present in rinse-off hair colouring at up to 6.5% and other leave-on hair products at up to 3%, which are derived from the maximum use concentrations reported for ammonium carbonate in these products. Ammonium carbonate is known to consist of ammonium bicarbonate [NH_4HCO_3] and ammonium carbamate [$NH_4CO_2NH_2$], according to the Food Chemicals Codex (CIR 2017; US FDA 2020).

The chemical has reported domestic uses in washing and cleaning products.

The chemical has reported commercial uses:

- as a processing aid (e.g. source of ammonia, propellant, pH regulator, etc.)
- in tableting processes (compression, extrusion, pelletisation, and granulation)
- as a component of agricultural fertilisers.

The chemical has reported site-limited uses:

- in chemical formulation and manufacture of bulk, large scale chemicals (including petroleum products)
- in manufacture of fine chemicals
- in pulp and paper products
- as an ammoniating agent
- as an intermediate in the production of urea
- as a decomposition stabiliser
- as a component in processes of exhaust emission denitrification.

The chemical has reported non-industrial uses in food, biocidal or pesticide products (such as a synergist in aluminum phosphide fumigant formulations, a fire-suppressing and/or warning agent).

Existing Australian regulatory controls

Public

No specific restrictions have been identified.

Workers

No specific restrictions have been identified.

At the time of this evaluation, the chemical is not listed in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia).

International regulatory status

Exposure standards

Ammonium carbamate has the following workplace exposure standards (NIOSH & ACGIH cited in New Jersey 2002; US NOAA 2019):

- 8-hour or 10-hour time-weighted average (TWA): 25 ppm (as NH_3; the chemical decomposes in air releasing ammonia up to 44% of the chemical by weight)
- short term exposure limit (STEL) and threshold limit value (TLV-Ceiling) = 35 ppm (as NH_3).

United States of America

The CIR (2017) review determined that ammonium carbonate (including ammonium carbamate) is safe at the current use and concentration in cosmetics when formulated to be non-irritating. However, eye and respiratory irritant effects from incidental eye contact and/or inhalation (from spray and loose-powder cosmetic products) cannot be ruled out for some known use concentrations.

Health hazard information

Toxicokinetics

The chemical is expected to be readily absorbed through mucous membranes via oral and inhalation routes, as well as through skin contact (ATSDR 2004; EFSA 2011). Ammonium carbamate was shown to penetrate into the stratum corneum of the porcine skin (CIR 2017; Novotny et al. 2011).

Following absorption, the chemical is rapidly hydrolysed to ammonium carbonate [$(NH_4)_2CO_3$], which further decomposes to ammonium bicarbonate [NH_4HCO_3], then to carbon dioxide, water and two molecules of ammonia [NH_3]. These reaction products, including ammonium [NH_4^+] and bicarbonate [HCO_3^-] ions, are also produced endogenously and exist in all tissues at equilibrium, which is pH-dependent, as below:

$$NH_4CO_2NH_2 + H_2O \leftrightarrow (NH_4)_2CO_3 \leftrightarrow NH_4HCO_3 + NH_3 \leftrightarrow CO_2 + H_2O + 2NH_3$$

Ammonia is then transformed to urea by the Krebs urea cycle in the liver and subsequently excreted via the kidney. Mammals may excrete small amounts of ammonia directly into the urine and less than 1% of the total ammonia in the faeces (EFSA 2011). Clearance of carbon dioxide from the body is primarily through exhalation (Patel et al. 2021).

Acute toxicity

Oral

Based on the available data, the chemical has moderate acute oral toxicity with reported median lethal doses (LD50) of less than 2000 mg/kg bw in rats, warranting hazard classification (see **Recommendation** section).

In an acute oral toxicity study similar to the OECD Test Guideline (TG) 401, Wistar rats (5/sex/dose) were treated by gavage with a single dose of ammonium carbamate. The LD50 values for both sexes were in the range 681–1470 mg/kg bw. Sublethal signs of toxicity included poor general state, apathy, staggering and dyspnoea (NTRL; REACH).

In another study in rats, the reported oral LD50 was 1380 mg/kg bw. Mortality occurred within 30 minutes of exposure and clinical signs of toxicity included apathy, convulsions and accelerated respiration (CIR 2017; REACH).

Dermal

Based on the available data, the chemical is expected to have low acute dermal toxicity. The dermal LD50 in rats is greater than 5000 mg/kg bw. Signs of irritation were noted, including erythema, oedema, scabbing and necrosis.

In an acute dermal toxicity study conducted in accordance with the OECD TG 402, Crl:CD(Sprague Dawley) rats (5/dose/sex) were treated with a 24-hour semi-occlusive application of ammonium carbamate to clipped, unabraded skin. The LD50 was greater than 5000 mg/kg bw. Irritation effects were observed, including slight to severe (score 1–4) erythema, eschar, slight to moderate (score 1–3) oedema, scabbing, necrosis, exfoliation, and desquamation. Erythema, eschar and scabbing persisted in 1/5 male and 2/5 female rats up to 14 days at study termination (CIR 2017; REACH).

Inhalation

No inhalation data are available for ammonium carbamate. On the basis that the chemical consists of ammonia (43.6%) and carbon dioxide (56.3%), its acute inhalation toxicity is expected to be attributable to those components that may be irritating to nose, throat, respiratory tract and lungs at high levels of exposure (CIR 2017; PubChem; US NOAA 2019).

Corrosion/Irritation

Skin irritation

Based on the weight of evidence from available data, the chemical may be irritating to the skin, particularly after prolonged exposure.

In an in vitro EpiDerm skin corrosion and irritation study (REACH) conducted in accordance with the OECD TG 431, the chemical was non-corrosive based on the cell viability measurements of 98% and 18% after 3 and 60 min exposures, respectively (OECD TG 431 criteria for skin corrosion refer). In a skin irritation test, the mean cell viability was 8% after 60 min exposure. Given the chemical is non corrosive and with reference to the cut-off value of less than or equal to 50% for cell viability (refer to OECD TG 439 skin irritation criteria), the chemical was considered irritating to skin according to the GHS Category 2.

In the acute dermal toxicity (above), irritation effects were noted after 24-hour exposure and up to 14 days although erythema and scabbing persisted only in 3/10 or 30% of the animals (CIR 2017; REACH).

In an acute dermal irritation/corrosion study conducted in accordance with the

OECD TG 404, New Zealand White rabbits (3 animals) were treated with the chemical under semi-occlusive and intact skin conditions for up to 4 hours. There were no signs of dermal irritation up to 72 hours after patch removal (REACH).

In a non-guideline acute dermal irritation study, Vienna white rabbits (2 animals) were treated with a 40% or 80% aqueous solution of ammonium carbamate for up to 15 minutes under occlusive conditions. Slight erythema was observed, which reversed within 24 hours (REACH).

Eye irritation

Based on the available data, the chemical has the potential to cause serious eye damage, warranting hazard classification (see **Recommendation** section).

In an ex vivo eye corrosive test conducted in accordance with the OECD TG 437 (bovine corneal opacity and permeability (BCOP)), the chemical at 10% or 20% produced in vitro irritancy scores (IVIS) of 113.3 and 128.7, respectively (REACH). With reference to the prediction criterion IVIS greater than 55, the chemical is considered to cause serious eye damage according to the GHS Category 1 (OECD TG 437).

In an ex vivo eye corrosive test conducted in accordance with the OECD TG 438 (hen's egg-chorioallantoic membrane (HET-CAM)), the chemical at 10% and 100% (undiluted) both produced responses falling into class IV for isolated chicken eyes (ICE) (REACH). On this basis, the chemical is considered as causing irreversible effects on the eye according to the GHS Category 1 (OECD TG 438).

In an acute eye irritation/corrosion study conducted in accordance with the OECD TG 405, the chemical produced corneal opacity that had not fully reversed within 21 days in 1/3 rabbits. In addition, eye irritation responses were reported in 2/3 animals with mean scores for corneal opacity = 2; iritis = 1; conjunctival redness = 2.67; chemosis = 1; and conjunctival discharge = 1.67 (REACH). On this basis, the chemical is deemed to be potentially a severe eye irritant according to GHS Category 1 (OECD TG 405).

Sensitisation

Skin sensitisation

Limited data are available. Given its rapid decomposition to endogenously occurring substances following absorption, the chemical is not expected to have skin sensitisation potential.

In a local lymph node assay (LLNA) conducted in accordance with the OECD TG 429, female CBA/J mice (5/dose) were treated on the ear with ammonium carbamate at 0, 10, 25 or 50% for 3 consecutive days. Vehicle and positive controls were conducted in parallel with the test chemical. No irritation or clinical toxicity were observed. Non-dose dependent stimulation indices (SI) of 1.1, 1.2 and 0.6 were reported for the tested concentrations, respectively. The chemical was not considered to be a skin sensitiser (REACH).

Repeat dose toxicity

Limited data are available for ammonium carbamate.

Long-term inhalation of ammonium carbamate (containing 43.6% ammonia) may cause laryngitis or bronchitis with cough, phlegm and shortness of breath (New Jersey 2002; PubChem Ammonia).

Given ammonium carbonate [$(NH_4)_2CO_3$] is a mixture of ammonium bicarbonate [NH_4HCO_3] and ammonium carbamate [$NH_4CO_2NH_2$], and that these chemicals share similar uses as buffering agents in cosmetic products (CIR 2017), these substances are expected to share similar toxicokinetic (see above) and toxicological profiles following repeated oral exposure.

Based on limited data available for ammonium carbonate and ammonium bicarbonate—the hydrolysis products of ammonium carbamate, together with data on related ammonium salts (ammonium chloride) and carbonate salts (sodium and potassium carbonate and bicarbonate), the JECFA (1982) considered that the dietary levels of ammonium carbonate and bicarbonate from use of food additives are extremely small compared with the levels required to alter acid-base balance or cause physiological pH changes, and as such they pose no toxicological hazard. Also, the JECFA advised that establishment of an Acceptable Daily Intake (ADI) of these ammonium salts for humans was not deemed necessary.

Ammonium carbonate and ammonium bicarbonate are also listed as 'Generally Recognized As Safe (GRAS)' for use as a pH control agent in food by US FDA (2020).

With regard to ammonia—the end metabolised product of ammonium carbamate, the EFSA (2011) considered that given the human body has intrinsic detoxification systems, the dietary levels of ammonia from use of food flavourings do not raise any toxicological concern.

Genotoxicity

Negative results were reported for ammonium carbamate in vitro mutagenicity tests. In vivo data are not available.

The chemical was negative in:

- 2 bacterial reverse mutation assays (OECD TG 471) in *Salmonella typhimurium* TA1535, TA1537, TA 98, TA 100, and *Escherichia coli* WP2 uvr A, with or without metabolic activation at up to 5000 µg/plate (REACH)
- a mammalian cell gene mutation assay (OECD TG 476) using Chinese hamster ovary (CHO)'s hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus, with or without metabolic activation at up to 800 µg/ml or 10 mM (REACH).

Carcinogenicity

When in systemic circulation, ammonium carbamate is readily converted to endogenously occurring substances, the bicarbonate and ammonium ions. Therefore, ammonium carbamate is not expected to be carcinogenic.

Reproductive and developmental toxicity

When in systemic circulation, ammonium carbamate is readily converted to endogenously occurring substances, the bicarbonate and ammonium ions. Therefore, ammonium carbamate is not expected to be toxic to reproduction and development.

References

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