Ammonium chloride ((NH4)Cl): Human health tier II assessment

12 September 2013

CAS Number: 12125-02-9

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.

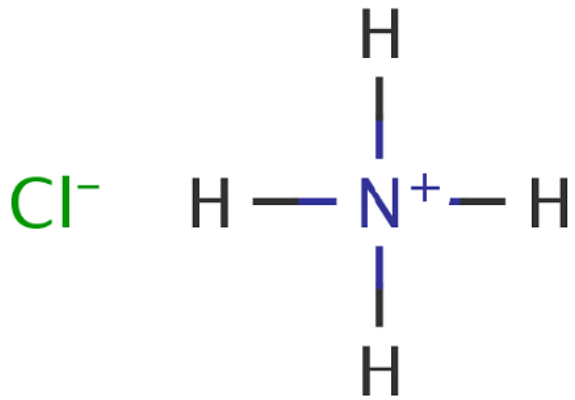
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	amchlor ammoneric ammonium muriate salmiac sal ammoniac
Structural Formula	
Molecular Formula	ClH4N
Molecular Weight (g/mol)	53.49
Appearance and Odour (where available)	An odourless, white, fine or coarse crystalline powder.
SMILES	N{+}.Cl{-}

Import, Manufacture and Use

Australian

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of between 1000 and 9999 tonnes.

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported commercial use:

- as a flux agent for casting.

The chemical has reported site-limited use:

- as a laboratory chemical.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; the American Cleaning Institute (ACI) cleaning product ingredient inventory; and other data sources via eChemPortal including the OECD High Production Volume (OECD HPV) chemical program, the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), the Finnish Environment Institute and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB):

The chemical has reported cosmetic use as a:

- fragrance ingredient;
- buffering and masking agent; and
- viscosity controlling agent.

The chemical has reported domestic use including:

- in paints, lacquers and varnishes;
- in cleaning/washing agents;
- in flame retardants and extinguishing agents; and
- as an adhesive and binding agent.

The chemical has reported commercial use including:

- as a cotton desiccant;
- as a pH regulation agent, e.g. acidifying agent;
- in flux agents for casting and joining, e.g. in zinc and tin plating;
- in dry battery manufacturing;
- in explosives manufacturing;
- as a surface treatment, e.g. etching solutions in printed circuit board manufacturing;

- as a fixing agent, e.g. mordant for dyes and printing; and
- as a process regulator, e.g. hardener for formaldehyde-based adhesives.

The chemical has reported site-limited use including:

- in the manufacture of laboratory chemicals, e.g. ammonia compounds.

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

Xn; R22 (Harmful if swallowed)

Xi; R36 (Irritating to eyes)

Exposure Standards

Australian

The chemical (fume) has an exposure standard of 10 mg/m^3 time weighted average (TWA) and a 20 mg/m^3 short-term exposure limit (STEL).

International

The following exposure standards for the chemical (fume) are identified (Galleria Chemica).

Time weighted average (TWA): 10 mg/m^3 [Belgium, Bulgaria, Canada, China, Denmark, France, Greece, Iceland, Ireland, Norway, Poland, South Africa, Spain, United Kingdom and USA (National Institute for Occupational Safety and Health—NIOSH, Occupational Safety and Health Administration—OSHA)].

TWA: 3 mg/m^3 [Switzerland]

Short-term exposure limits (STEL): 20 mg/m^3 [Belgium, Canada, China, Greece, Ireland, Poland, South Africa, Spain, United Kingdom and USA (National Institute for Occupational Safety and Health—NIOSH, Occupational Safety and Health

Administration—OSHA)].

Health Hazard Information

Both of the constituent ions (chloride anion and ammonium cation) of this chemical are also found in chemicals which have been assessed to be of low concern by NICNAS (NICNAS a; NICNAS b; NICNAS c). However, for this chemical, the high concentration of the slightly acid ammonium ion may give rise to potential for local effects not shared with other ammonium or chloride salts.

Toxicokinetics

The chemical is reported to be absorbed rapidly from the gastrointestinal tract within 3–6 hours following oral ingestion. It is then metabolised in the liver to form urea and hydrochloric acid, both of which are detectable in urine. Large doses of the chemical are reported to acidify urine (HSDB; OECD 2003; REACH).

Acute Toxicity

Oral

The chemical is classified in Australia as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). The available data support this classification.

The chemical is reported to be slightly acutely toxic through oral route of exposure. The oral median lethal doses (LD50) in Wistar rats was reported to be 1410 mg/kg bw. At doses >1000 mg/kg bw, signs of toxicity included dyspnoea (shortness of breath), apathy, abnormal posture and staggering (OECD 2003; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Signs of toxicity reported in humans exposed to the chemical at large doses include nausea, vomiting, thirst, headaches, hyperventilation, progressive drowsiness, metabolic acidosis (the build-up of acid and hydrogen ions in the body), and hypokalaemia (potassium deficiency) (OECD 2003; REACH).

Corrosion / Irritation

Skin Irritation

The chemical was reported to not be irritating to the skin (abraded and unabraded) of New Zealand White rabbits, following application of 0.5 g to six animals, for a period of 24 hours using an occlusive patch. Animals were observed at 24, 48 and 72

hours after removal of the patch. Erythema (redness of skin) was reported in some of the animals at 24 hours. However, no signs of irritation were observed 48 hours after the patch was removed (REACH).

In another skin irritation study, Vienna White rabbits were exposed to 2 g of the chemical, under occlusive conditions on shaved skin for 1, 5, 15 min (two animals per exposure period) or 20 hours (four animals), and observed over eight days. While slight erythema was reported in animals exposed to the chemical for =15 mins, the effect was reversible within 72 hours. In animals exposed to the chemical for 20 hours, distinct irritation, primarily expressed by erythema, was observed; the effect was not reversible by the end of the eight-day observation period (OECD 2003; REACH).

While there is an indication of potential for skin irritancy, there is insufficient consistent evidence to classify the chemical as a skin irritant.

Eye Irritation

The chemical is classified in Australia as hazardous with the risk phrase ‘Irritating to eyes’ (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification.

The chemical was irritating to the eyes of Vienna White rabbits that were administered 50 mg of the chemical (powdered form) into the conjunctival sac of the eye. All effects were still observable 72 hours after exposure, but were not visible by the end of the eight-day observation period (OECD 2003; REACH).

In a second study, a 1 % aqueous solution of the chemical was reported to be slightly irritating to the eyes of rabbits. Substantial hyperaemia (increased blood flow) of the iris was reported. However, effects were reversible by end of the exposure period (OECD 2003).

Sensitisation

Skin Sensitisation

The chemical was not found to be sensitising to the skin in a guinea pig maximisation test.

Female Pirbright-White guinea pigs were administered a 5 % solution of the chemical (in saline) by an intradermal injection. Eight days later, 0.5 mL of a 25 % solution of the chemical was topically applied under an occlusive patch for 48 hours to assess topical induction exposure; only slight oedema was reported.

When challenged 13 days later with 0.5 mL of a 10 % solution of the chemical for 24 hours (occlusive patch), 2/20 animals were reported to have positive reactions (erythema) visible 24 and 48 hours after removal of the occlusive patch. The result (10 %) does not meet the criteria for skin sensitisation as a positive response in ≥30% of the animals was not achieved (OECD 2003; REACH).

Repeated Dose Toxicity

Oral

In a repeated dose toxicity study (similar to OECD Test Guideline (TG) 408), male and female Wistar rats (10/sex/group) were administered the chemical in their diet at 2 % (1695.7 mg/kg bw/day) and 4.1 % (3372.6 mg/kg bw/day) for 13 weeks (REACH). While reduced body weights were reported, no signs of systemic toxicity were observed. The no observed adverse effect level (NOAEL) for this study was reported to be 1695.7 mg/kg bw/day.

In an additional study, male Sprague Dawley (SD) rats (10/group) were administered the chemical in their diet at 12300 ppm (equivalent to 684 mg/kg bw/day) for 70 days. It was reported that the chemical caused no effect on clinical signs, body weights or food consumption (OECD 2003; REACH). No findings were reported following histopathological examination of the stomach, kidneys and bladder. Decreased urinary pH was reported in the treatment group animals (pH of 6.0) compared with control

group animals (pH ≥7.56), in addition to significantly increased urinary calcium levels. However, no crystals were detected in the urine. The NOAEL for this study was reported to be 684 mg/kg bw/day.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

A 58-year-old female ingested 6 g of the chemical on a daily basis for a period of six months as a urine-acidifying agent. The patient had a history of renal calculi and urinary tract infection. The combination of decreased renal function and hydrogen ion loading caused severe systemic acidosis. It was reported that the female presented to the hospital emergency department with exhaustion and shortness of breath.

In another case study, 15 g of the chemical was ingested daily for six months as a diet control by an 18-year-old female. It was reported that she became nauseated and weak with transient hyperventilation, and was admitted to hospital. Prior to her hospital admission, during a period of 48 hours, she consumed 82 grams of this substance and developed nausea and a headache. The female vomited and gradually became drowsy, confused and lapsed into a comatose state.

Genotoxicity

The chemical was reported to be negative in bacterial point mutation tests, positive in one of two in vitro mammalian chromosome aberration tests, and negative in one in vivo micronucleus assay in mice.

In vitro

The chemical was reported to not be mutagenic in *Salmonella typhimurium* bacterial strains TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537 and TA 1538 TA1538, and *Escherichia coli* strainWP2uvrA with and without metabolic activation (OECD 2003; REACH).

The chemical increased structural chromosomal aberrations in Chinese hamster lung cells (CHL/IU) with metabolic activation (OECD 2003; REACH). However, it was reported negative for chromosomal aberration in Chinese hamster ovary (CHO) cells with and without metabolic activation (REACH).

In vivo

In the only available in vivo genotoxicity study, the chemical was reported to not induce micronuclei in bone marrow in male mice (six/dose) following either a single intraperitoneal (i.p.) injection of 0, 62.5, 125, 250 or 500 mg/kg bw/day, or four i.p. injections of 0, 31.3, 62.5. 125 or 250 mg/kg bw/day at 24-hour intervals (OECD 2003; REACH).

While there is an indication of genotoxicity based on one in vitro mammalian cell study, the weight of evidence across the available studies indicates that the chemical is not genotoxic.

Carcinogenicity

The chemical is not expected to be a carcinogen.

In a carcinogenicity study in male and female rats (OECD TG 451), the chemical induced chronic metabolic acidosis and a reduction in body weights. However, no carcinogenic effects were reported (REACH).

In another study in rats and mice, the chemical was found to not be a promoter of carcinogenic effects induced by other substances such as N-butyl-N-(4-hydroxybutyl) nitrosamine by acidification of the urinary system. While a decrease in urine pH was reported, there were no increases in the incidences of bladder tumour, hyperplasia (increased cell production in a normal tissue or organ) or calculi (abnormal stone formed by an accumulation of mineral salts) (OECD 2003).

Reproductive and Developmental Toxicity

The chemical is not expected to be a reproductive or developmental toxin.

It was reported that no developmental toxic or teratogenic effects were found in a non-guideline study in SD rats exposed to the chemical by oral administration at 8.9 mg/kg bw/day on days 7–10 of gestation. No foetal malformations or foetal deaths were reported at day 20 of gestation. While inhibited foetal growth was reported, this was attributed to maternal effects of metabolic acidosis (OECD 2003).

In another non-guideline study, SD rats were orally administered the chemical at 4.73 mg/mL (in drinking water) and 421 mg/kg bw (in feed) on days 7–11 of gestation. There were no treatment-related effects on the number of live foetuses per litter, resorptions or foetal body weights. No teratogenic effects were observed. A NOAEL of 421 mg/kg bw/day was reported for maternal toxicity and teratogenicity (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include harmful systemic effects following acute oral exposure. The chemical may also cause eye and skin irritation.

Public Risk Characterisation

The chemical is not currently listed in the Poisons Standard (SUSMP) and there are no restrictions on the use of this chemical in Australia.

Although the use of this chemical in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic and/or domestic products overseas (including surface treatments, arts and crafts, personal care products and home maintenance products). Available information indicates that the chemical is used in home maintenance products overseas at concentrations between 1 % to 10 %, and in personal care products at ≤3 % (U.S. National Library of Medicines), which are within concentration limits unlikely to be of concern.

As concentrations ≥20 % are considered to cause eye irritation (Safe Work Australia), the public health risk posed by normal use of cosmetic or domestic products containing the chemical is not expected to be unreasonable.

Occupational Risk Characterisation

Given the critical health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise 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.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No

further assessment is required.

Regulatory Control

Public Health

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

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 hazards 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	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)

[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 label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from 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:

- 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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