Nitric acid, ammonium salt: Human health tier II assessment

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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.

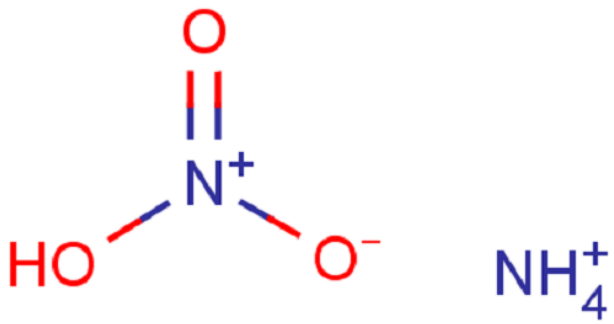
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Ammonium nitrate Nitram German salpeter Emulite Varioform I
Structural Formula	
Molecular Formula	H3N.HNO3
Molecular Weight (g/mol)	80.0
Appearance and Odour (where available)	Odourless, transparent, deliquescent crystals or white to grey granules.
SMILES	N(=O)(=O)O{-}.N{+}

Import, Manufacture and Use

Australian

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

The chemical has reported commercial use in explosives and oxidising agents.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of between 100000 and 999999 tonnes.

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; and other data sources via eChemPortal including the OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use:

- as a buffering agent; and
- in hair dyes, tints and colourings.

The chemical has reported domestic use including in:

- paints, inks and pigments, e.g. in yellow printer inks;
- fertilisers;
- cleaning and washing agents; and
- adhesives and binding agents.

The chemical has reported commercial use including:

- as a cotton desiccant;
- as a photochemical;
- in bleaching agents;
- as an electroplating agent;
- as a process regulator;
- in freezing agents;
- in the manufacture of fireworks, safety explosives, matches and pyrotechnics; and
- in surface treatments.

The chemical has reported site-limited use including:

- as an intermediate; and
- in the manufacture of laboratory chemicals, e.g. nitrous oxide (laughing gas).

Restrictions

Australian

While no known restrictions have been identified, nitrates are listed as 'Restricted hazardous chemicals' under the *Australia Work Health and Safety Regulations 2011*, with restrictions for use in wet abrasive blasting.

The chemical is also included in the list of 96 'Chemicals of Security Concern' identified by the Council of Australian Governments (COAG). This listing has an additional note for Security Sensitive Ammonium Nitrate (SSAN), where specific state based restrictions apply: 'ammonium nitrate, ammonium nitrate emulsions and ammonium nitrate mixtures containing greater than 45 per cent ammonium nitrate excluding solutions' (SafeWork SA).

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards were identified (Galleria Chemica):

Time weighted average (TWA): 10 mg/m^3 [Canada, Ireland, Spain].

TWA: 5 mg/m^3 [Bulgaria, USA]

The chemical is also listed under Rule 7 (Industrial Activity) of India's Manufacture, Storage and Import of Hazardous Chemical Rules - Schedule 3, for which a threshold quantity of 350 tonnes applies: 'This applies to ammonium nitrate and mixtures of ammonium nitrate where the nitrogen content derived from the ammonium nitrate is greater than 28% by weight and aqueous solutions of ammonium nitrate where the concentration of ammonium nitrate is greater than 90% by weight.'

Health Hazard Information

Both of the constituent ions (nitrate 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, both constituent ions are present at high concentrations and the combination of the slightly acid ammonium ion and the potentially oxidising nitrate ion may give rise to potential for local effects not shared with other ammonium or nitrate salts.

Toxicokinetics

In a study on 12 human volunteers who orally ingested 7-10 g of the chemical, it was reported that, following intestinal absorption, the ammonium ions were converted to urea through the liver and then excreted in urine. Increased levels of nitrate in blood, urine and saliva were detected after ingestion of the chemical; nitrate and nitrite levels in saliva ranged from 4 to 43 mmol/L 2-6 hours after ingestion. An average of 75 % of administered nitrate was reported to be excreted in urine within 24 hours (HSDB; OECD 2007).

Acute Toxicity

Oral

The chemical is reported to be of low acute toxicity through oral route of exposure. The lowest acute oral median lethal dose (LD50) in rats was reported to be >2000 mg/kg bw (OECD 2007; REACH).

Dermal

The chemical is reported to be of low acute toxicity through dermal route of exposure. The LD50 values in rats were reported to be >5000 mg/kg bw (OECD 2007).

Inhalation

The chemical is reported to be of low acute toxicity through inhalation route of exposure. A non-guideline study in rats exposed to the chemical, reported a median lethal concentration (LC50) value of >88.8 mg/L. No significant toxicological effects were observed (REACH).

Observation in humans

No oral toxicity was reported in 12 adult volunteers administered a single oral dose of 150 mg/kg bw of the chemical. No haematological effects, increase of methaemoglobin or formation of N-nitroso compounds were reported (OECD 2007; REACH).

Corrosion / Irritation

Skin Irritation

The chemical was not found to be a skin irritant in New Zealand White rabbits when tested according to OECD Test Guideline (TG) 404.

Rabbits were exposed to 0.5 g of the chemical under occlusive conditions moistened with water, over four hours and observed during a 72 hour period (at 1, 25, 48 and 72 hours). It was reported that exposure to the chemical resulted in low Draize scores with no reported oedema (swelling) or erythema (redness) (REACH).

Eye Irritation

In an OECD guideline study (TG 405), 100 mg of the chemical was applied to the eyes of rabbits over a 24 hour exposure period. It was reported that animals tested had an average score for redness of the conjunctivae of >2.5 during the first 3 days

after exposure. The effects were reported to be fully reversible within 7-10 days (REACH).

In another study in rabbits, the chemical was reported to be moderately irritating to the eyes, causing conjunctival effects and mild iritis (inflammation), although no corneal effects were noted. The effects were reported to be fully reversible after 7 days (REACH).

There is sufficient evidence to classify the chemical as an eye irritant (R36; irritating to eyes).

Sensitisation

Skin Sensitisation

While no data are available for this chemical, no significant adverse effects were reported following skin sensitisation exposure to another nitrate compound which contained both of the constituent ions of the chemical.

In a skin sensitisation study (local lymph node assay: OECD TG 429), mice were exposed to calcium ammonium nitrate at doses of 0 %, 10 %, 25 % and 50 % (five animals per/dose) on three consecutive days. The test groups had calcium ammonium nitrate applied directly to the dorsal surface of both ears.

While erythema was shown to occur in all animals at 50 % and in one animal at 25 %, the stimulation index (SI) for skin sensitisation was reported to be <3. Therefore the chemical is not considered to be a skin sensitiser. Additionally, no change in body weight, no mortality, no systemic toxicity or oedema was reported for any treatment group of animals (REACH).

Repeated Dose Toxicity

Oral

While no data are available for this chemical, no significant adverse effects were reported following repeated oral exposure to potassium nitrate or ammonium chloride (OECD 2007; REACH; NICNAS b).

In an OECD guideline study (TG 422), male and female rats (five/sex/dose) were exposed to potassium nitrate through oral gavage for 28 days at 0, 250, 750 and 1500 mg/kg bw/day. No deaths or treatment related clinical signs were reported. There were no changes in body weight, food consumption or motor function. An increase in blood levels of urea, nitrogen and phosphorous were reported to be non-treatment related, due to the absence of renal dysfunction. The NOAEL for this study was reported to be 1500 mg/kg bw/day (OECD 2007; REACH).

In a repeat dose oral toxicity study (TG 408), ammonium chloride was administered to male and female Wistar rats (10/sex/group) via oral feed at 2 % (1695.7 mg/kg bw/day) and 4.1 % (3372.6 mg/kg bw/day) for 13 weeks. While reduced body weights were reported, no signs of systemic toxicity were observed. The NOAEL for this study was reported to be 1695.7 mg/kg bw/day (NICNAS b).

Inhalation

In a 4-week, repeat dose inhalation study (OECD TG 412), male Sprague Dawley (SD) rats and Hartley guinea pigs were exposed to 1 mg/m^3 of the chemical for six hours/day, five days/week. No treatment related effects on body weight, lung volume or histologic structure of ciliated epithelial cells (hair-like fringed layers of cells that line the respiratory tract) were reported. The no observed adverse effect concentration (NOAEC) was reported to be ≥1 mg/m^3 (OECD 2007; REACH).

In another repeat dose inhalation study, male SD rats (10 rats/dose) were exposed to the chemical via inhalation (nose/head only) at doses of 26-185 mg/m^3 for five hours/day, five days/week, over two weeks. No significant differences in body weight were reported when compared to controls. Irritation in the nostrils of treated animals was reported, although concentrations at which these effects occurred were unclear. The systemic no observed adverse effect concentration (NOAEC) for this study was reported to be ≥185 mg/m^3 (REACH).

Observation in humans

A case study in humans reported that no systemic oral toxicity was observed in 23 patients who had taken up to 9 g of the chemical daily for an undefined period of time. The chemical was taken as a preventive treatment for calcium phosphate renal stones (OECD 2007; REACH).

Another case study reported oral ingestion of the chemical (single doses between 64 and 234 grams) by five patients which did not cause severe toxic effects. However, some patients experienced gastritis (inflammation of the lining of the stomach), slightly increased methaemoglobin levels, and mild hypertension (high blood pressure) (OECD 2007; REACH).

Genotoxicity

The chemical is not expected to be genotoxic.

The chemical tested negative in a number of in vitro genotoxicity tests. These included bacterial reverse mutation assays (OECD TG 471) using *S. typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 1000 (OECD 2007; REACH).

Carcinogenicity

While no data are available for this chemical, no carcinogenic effects were reported following exposure to sodium nitrate and ammonium chloride (REACH; NICNAS b).

In a carcinogenicity study in rats (50/group/sex), sodium nitrate was administered via the diet at 0 %, 2.5 %, and 5 % for 104 weeks. The number of animals with tumours were reported to be 94 %, 100 % and 96 % for males; and 92 %, 86 % and 80 % for females, for each respective dose group. No increased incidence of tumours in treatment group animals was reported when compared with control animals (Maekawa et al.; OECD 2007).

It is noted that nitrates taken up in food may be involved in the formation of N-nitroso compounds that are known mutagens or carcinogens. However, no positive relationship has been found between cancer incidence and nitrate intake in several epidemiological studies (OECD 2007). Additionally, formation of N-nitroso compounds were not observed following ingestion of the chemical in humans (refer to sections **Observations in Humans under Acute Toxicity and Repeat Dose Toxicity**).

In another study (OECD TG 251), ammonium chloride was not reported to be carcinogenic in rats. While chemical induced chronic metabolic acidosis was reported, no treatment related carcinogenic effects were observed (NICNAS b).

Reproductive and Developmental Toxicity

While no data are available for this chemical, no reproductive or developmental effects were reported following oral exposure to potassium nitrate and ammonium chloride (OECD 2007; REACH; NICNAS b).

In a combined reproduction/developmental toxicity study (OECD TG 422), male and female SD rats (five males/group/dose; 10 females/group/dose) were exposed to potassium nitrate via oral gavage at 0, 250, 750 and 1500 mg/kg bw/day for 28 days (males) and from 14 days pre-mating until day four of lactation (females). No deaths or treatment related effects on mating performance, fertility, gestation length, gestation index, litter size, offspring survival, sex ratio or offspring body weight were reported. There were no reported changes in body weight or food consumption. The NOAEL for reproduction was reported to be 1500 mg/kg bw (OECD 2007; REACH).

It was reported that no developmental toxic or teratogenic effects were found in a non-guideline study in SD rats exposed to ammonium chloride solution via 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 (NICNAS b).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the local effect of eye irritation.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used overseas as a buffering agent in cosmetics (CosIng) and in personal care products, where the general public may be exposed to the chemical through dermal and/or inhalation routes.

However, no cosmetic products containing the chemical are listed on the US National Library of Medicine (NLM) Household Products Database. As the chemical is reported to have potential buffering agent use, it is expected that exposure would be to low concentrations, which would result in minimal risk. Considering this, in addition to no reported cosmetic use of the chemical in Australia, the likelihood of public exposure to cosmetic products containing the chemical is low.

While use of the chemical in domestic products in Australia is not known, it is reported to be used in domestic products overseas. The only available information in regard to concentration in domestic products is from the US National Library of Medicine's Household Products Database, indicating use in liquid form domestic ink cartridge products at $\leq$3 % and fertilisers and potting mix in the form of soil, powder and granules.

Currently, there are no restrictions in Australia on using this chemical in cosmetics but there are specific, state based restrictions (on security grounds) on the use of the chemical in domestic products, including fertilisers. However, given the available information on the use of the chemical in cosmetic and/or domestic products, it is unlikely that the public will be exposed to the chemical at appreciable concentrations. Therefore, the risk to the public is not considered 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.

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

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]
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:

- 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;
- 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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