Nitrous acid, sodium 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.

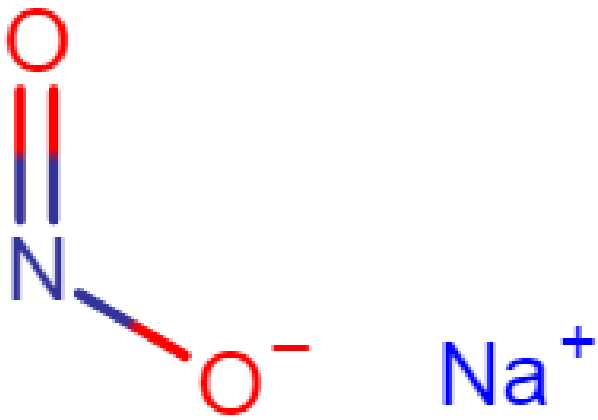
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	sodium nitrite
Structural Formula	
Molecular Formula	HNO2.Na
Molecular Weight (g/mol)	68.99
Appearance and Odour (where available)	White or slightly yellowish crystals, pellets, sticks or powder.
SMILES	N(=O)O{-}.[Na]{+}

Import, Manufacture and Use

Australian

The chemical was reported to have domestic use in paints as a rust inhibitor at concentrations around 0.1 %.

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD) Screening information data set International Assessment Report (SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use as a corrosion/rust inhibitor (preventing corrosion of materials used to pack or produce cosmetics) (CosIng, Personal Care Products Council).

The chemical has reported domestic uses (SPIN), including:

- in adhesives or binding agents;
- in paints, lacquers and varnishes;
- in cleaning or washing agents.

The chemical has reported commercial uses, including:

- in dyeing and printing textiles and fabrics;
- for bleaching flax silk and linen;
- as a process regulator (heat transfer and storage);
- in anti-freezing and anti-static agents;
- as a construction material additive;
- in explosives;
- as a corrosion inhibitor for multipurpose greases;
- as a photographic chemical;
- for surface treatment (metal treatment); and
- as a lubricant and additive (component of detinning solution and multipurpose greases);

The chemical has reported site-limited uses, including:

- in the manufacture of azo dyes, nitroso and isonitroso compounds;
- as an electroplating agent; and
- as a component of heat-transfer salts.

The chemical has reported non-industrial uses, including:

- in meat curing, colouring and preserving;
- therapeutic use as a vasodilator or antidote for cyanide poisoning; and
- in agricultural pesticides (pyramin).

The OECD states that 'the most common source of exposure of anthropogenic sodium nitrite to consumers is from its use in cured meat products' (OECD, 2005).

Restrictions

Australian

The chemical is listed in Schedules 2, 5, 6 and 7 of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2015).

The Schedule 2 listing is for therapeutic use (excluding when present as an excipient) of the chemical.

Schedule 5:

'SODIUM NITRITE in preparations containing 1 per cent or less of sodium nitrite **except**:

(a) in preparations containing 0.5 per cent or less of sodium nitrite;

(b) when present as an excipient in preparations for therapeutic use; or

(c) in aerosols.'

Schedule 6:

'SODIUM NITRITE in preparations containing 40 per cent or less of sodium nitrite **except**:

(a) when included in Schedule 2 or 5;

(b) in preparations containing 0.5 per cent or less of sodium nitrite;

(c) when present as an excipient in preparations for therapeutic use; or

(d) in aerosols containing 2 per cent or less of sodium nitrite.'

Schedule 7:

'SODIUM NITRITE **except**:

(a) when included in Schedule 2, 5 or 6;

(b) in preparations containing 0.5 per cent or less of sodium nitrite;

(c) when present as an excipient in preparations for therapeutic use; or

(d) in aerosols containing 2 per cent or less of sodium nitrite.'

Schedule 7 chemicals are described as 'Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply'. Schedule 7 chemicals are labelled with 'Dangerous Poison' (SUSMP, 2015)

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2015).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2015).

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down (The use of the chemical as a rust inhibitor is restricted to a maximum concentration in ready for use preparation to 0.2 %, and not to be used with secondary and/or tertiary amines or other substances forming nitrosamines);
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down; and

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 list of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.

Existing Work Health and Safety Controls

Hazard Classification

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

- T; R25 (acute toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standard is identified (Galleria Chemica):

An exposure limit of 0.1 mg/m^3 time weighted average (TWA) in Russia.

Health Hazard Information

The main toxic effects of the chemical are expected to be due to effects of the nitrite ion following systemic absorption. The nitrite ion is ubiquitous in the environment and exists as part of the nitrogen cycle. The main source of exposure to nitrite ion for humans is from sodium nitrite in food products (FSANZ, 2013), but nitrite is also found in human saliva and formed *de novo* in human intestines (NTP, 2001).

Toxicokinetics

Nitrite, nitrate and nitric oxide (NO) follow interconversion pathways depending on physiological conditions, and the metabolic processes for these chemicals are interdependent.

When nitrate is absorbed into the circulatory system, it is either secreted in the saliva (25 %) or reduced to nitrite (5 % of ingested dose) by mammalian nitrate reductase activity and intestinal bacteria. In blood, nitrite is again oxidised irreversibly by haemoglobin to nitrate, before excretion in urine. In vivo studies in mice have indicated that nitrite oxidation may also occur in the stomach prior to absorption (NTP, 2001; OECD, 2005). The favourable pathway for urinary excretion is mainly as nitrate, whereas urinary nitrite is detected in people with bacterial infections in the urinary tract (IARC, 2010).

In rats and mice, sodium nitrite is absorbed unchanged in the stomach following oral administration. In mice, 85 % of the dose disappears in 10 minutes, around 99.1–99.5 % of the orally administered dose in drinking water is eliminated in urine, with the remainder converted to nitrate. In rats, the absorption rate of nitrite in the GI tract is slower than in mice, and is 4.5 times greater than the rate of degradation. Sodium nitrite mixed in food remained in the stomach for up to five hours, with a half-life of 1.4 hours (NTP, 2001; IARC, 2010).

Nitrite reacts rapidly with haemoglobin to form methaemoglobin (metHb) which can reduce oxygen transport in the blood causing methaemoglobinaemia. This is the primary acute toxic effect of the chemical. In rats, a single oral dose of sodium nitrite at 0.15 g/kg bw caused elevated metHb concentrations (45–80 %) within one hour. If the animal survives, metHb concentrations revert back to normal after 24 hours. Plasma sodium nitrite concentrations are parallel to the metHb formation in rats (NTP, 2001; HSDB).

Nitrite also reacts readily with secondary amines and amides to form carcinogenic *N*-nitroso compounds in humans (NTP, 2001; OECD, 2005).

Sodium nitrite may react with phenolic antioxidants under acidic conditions to form compounds with genotoxic and carcinogenic properties (NTP, 2001).

Nitrite is one of the end-products from NO production. However, a reverse pathway where nitrite is converted to NO can occur in vivo under hypoxic acidic gastric conditions. The vasodilation properties of nitrite are postulated to be through conversion to NO, or a NO-containing compound that acts as a signal for smooth muscle relaxation (IARC, 2010; HSDB).

Acute Toxicity

Oral

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

The median lethal dose (LD50) is 85 mg/kg bw in rats, 175–216 mg/kg bw in mice, and 186 mg/kg bw in rabbits. The primary acute toxic effect of the chemical in rats and mice is methaemoglobinaemia, and the secondary acute effects are vasodilation, relaxation of smooth muscle (see **Toxicokinetics**), and lowering of blood pressure. Other sublethal effects include diarrhoea, abdominal pain, decreased vitamin A levels in the liver, and functional disturbance of the thyroid (NTP, 2001; HSDB).

Dermal

No data are available.

Inhalation

The chemical does not have high acute toxicity in animal tests following inhalation exposure. Limited data from a rat study indicates a median lethal concentration (LC50) >0.1 mg/L.

In an acute inhalation toxicity study (non-guideline), rats were exposed (nose only) to sodium nitrite aerosols (dry particulates) for four hours, at 10 or 100 mg/m^3. Methaemoglobin levels were significantly increased above concurrent control values in females exposed to 10 mg/m^3 only, but not in males. This effect was not considered significant. No mortalities or other adverse effects were observed within the 14-day observation period (OECD, 2005).

Observation in humans

The primary toxic effect of the chemical in humans is methaemoglobinaemia. A normal concentration of metHb in humans is 0.5–3 %, and concentrations up to 10 % can occur without apparent clinical signs. Symptoms observed with increasing levels of metHb include cyanosis (at 10–15 %), progressive central nervous system effects (nausea, vertigo and lethargy) and dyspnoea (at 45–55%), abdominal pain, rapid fall in blood pressure, coma and convulsions, and high risk of mortality at >60 % (OECD, 2005; IARC, 2010; HSDB).

Many case reports are available with regard to ingestion of nitrite. The first symptoms of oral nitrite poisoning are reported to develop within 15–45 minutes. Symptoms related to nitrite poisoning and metHb formation following oral ingestion occurred at doses ranging from 0.4 to >200 mg/kg bw. The lowest oral acute lethal dose of nitrite in humans ranged from 27–255 mg/kg bw (as nitrite) (IARC, 2010; HSDB).

A 17-year old nurse who ingested a 1 g tablet of sodium nitrite (670 mg nitrite ion) died two hours after admission to the hospital, with a post mortem metHb level of 35 %. However, an adult survived without long-term adverse effects after ingestion of 9.7 g sodium nitrite. In another case of accidental ingestion of sodium nitrite, two children added these crystals in cups of tea at concentrations of 4900–5100 mg/L. MetHb levels of 77 % and 38 % were measured (OECD, 2005; HSDB).

Infants under 3 months old are particularly susceptible to methaemoglobinaemia, known as the blue baby syndrome. Foetal haemoglobin is more easily oxidised to metHb than adult haemoglobin. Infants also have reduced nicotinamide adenine dinucleotide (NADH) phosphate-dependent metHb reductase, and the lower production of gastric acid leads to a greater reduction of nitrate to nitrite. Many

case reports have indicated the development of metHb in babies after drinking water or fed spinach with high nitrate or nitrite content (IARC, 2010).

Human volunteers administered sodium nitrite intravenously (i.v.) produced a maximum metHb level of 7 % at a dose of 2.7 mg/kg bw, and 30 % after a dose of 8 mg/kg bw (HSDB).

A four year old boy was dermally treated all over with two liniment solutions containing the chemical at 30 g/L (Liniment A) and 140 g/L (Liniment B). Liniment A caused listlessness and vomiting. Application of Liniment B a few days later caused the boy to suffer from shock and severe cyanosis. The boy was hospitalised immediately but died after two hours in intensive care. His metHb level was found to be at 76 % (OECD, 2005).

Corrosion / Irritation

Skin Irritation

The chemical is a slight skin irritant in rabbits.

In a skin irritation study conducted according to the OECD Test Guideline (TG) 404, the chemical (500 mg) was applied (semi-occlusively) to the shaved backs of male New Zealand White rabbits (n = 6) for four hours, followed by observation up to three days. Slight irritation was observed one hour post-application, but these effects disappeared within 24 hours. The substance was not considered to be a skin irritant (OECD, 2005).

Eye Irritation

The chemical is a moderate eye irritant in rabbits. Although irritation scores are not available, the REACH Dossier has considered the chemical as a severe eye irritant based on this study.

In an eye irritation study (OECD TG 405), the chemical (100 mg) was instilled into the conjunctival sac of the left eye of female New Zealand White rabbits (n = 6), with observation up to 12 days. Three rabbits had their eyes washed with water for two to three minutes following exposure. All animals showed conjunctival effects, consisting of moderate redness, mild chemosis and severe discharge (irritation scores not available). These effects were reversible by 12 days. No corneal effects were observed. The chemical was reported to be a moderate eye irritant (OECD, 2005).

Observation in humans

The chemical is reported to be an eye irritant. Respiratory tract irritation can occur in patients who abuse volatile nitrites (HSDB).

Sensitisation

Skin Sensitisation

No data are available.

The OECD SIAR concluded that sensitisation potential is not expected as this substance is endogenously generated. Furthermore, no cases of sensitisation in humans have been reported (OECD, 2005).

Repeated Dose Toxicity

Oral

Based on the available data, the primary toxic effect of the chemical following repeated oral toxicity is methaemoglobinaemia.

In a repeated dose toxicity study conducted by the National Toxicology Program (NTP), groups of Fischer (F344) rats (n = 10/sex/dose) were administered the chemical in drinking water at concentrations of 0, 375, 750, 1500, 3000 or 5000 ppm (males: 30–310 mg/kg bw/day, females: 40–345 mg/kg bw/day), for 14 weeks. One female at 225 mg/kg bw/day died before the end of the study. MetHb levels were significantly elevated in all treated groups, and were dose-dependent. Effects observed included brown discolouration in the eyes and cyanosis of the mouth, tongue, ears, and feet at >200 mg/kg bw/day in males and at >130 mg/kg bw/day in females, significantly increased kidney and spleen weights at >200 mg/kg bw/day in males and at >225 mg/kg bw/day in females, decreased sperm motility in males at >115 mg/kg bw/day, increased reticulocyte counts and erythropoietic activity in both sexes at >200 mg/kg bw/day, and increased incidences of squamous cell hyperplasia in the forestomach of both sexes at the highest dose. A no observed adverse effect level (NOAEL) could not be determined (NTP, 2001; OECD, 2005).

In another study, B6C3F1 mice were administered the chemical in drinking water at concentrations of 0, 375, 750, 1500, 3000 or 5000 ppm (males: 90–990 mg/kg bw/day, females: 120–1230 mg/kg bw/day), for 14 weeks. In males, significantly decreased body weights and decreased sperm motility at 990 mg/kg bw/day, degeneration of testes at >750 mg/kg bw/day, and a slight decrease in water consumption at >345 mg/kg bw/day were observed. At the two highest doses, relative spleen weights in males and relative heart, kidney, liver, and spleen weights in females were increased compared with the controls. Oestrous cycles were significantly longer in females at 445 and 1230 mg/kg bw/day. Both sexes showed increased incidences of squamous cell hyperplasia in the forestomach at the highest doses, and extramedullary haematopoiesis of the spleen at >750 mg/kg bw/day in males, and at 1230 mg/kg bw/day in females. MetHb levels were not reported and no signs of metHb toxicity were observed (NTP, 2001).

In two-year chronic toxicity/carcinogenicity studies, metHb levels were measured in rats exposed to the chemical at 0, 750, 1500 or 3000 ppm for two weeks or three months. The levels increased at night when the rats were actively feeding and drinking and were low during the day when they were less active. No significant increase in metHb levels was observed in mice exposed to the same concentrations, when examined after 12 months. Based on the two-year studies, the NOAELs were determined as 130–150 mg/kg bw/day in rats, and 165–220 mg/kg bw/day in mice (NTP, 2001; OECD, 2005). Most of the prominent effects observed were related to carcinogenicity (see **Carcinogenicity**).

Another two-year study in male rats established a no observed effect level (NOEL) of 10 mg/kg bw/day (equivalent to 6.7 mg/kg bw/day nitrite) based on histopathological changes in the lungs and heart (dilatation of the bronchi with infiltration of lymphocytes and alveolar hyperinflation in lungs at >100 mg/kg bw/day and focal degeneration and fibrosis of the heart muscle at 350 mg/kg bw/day). MetHb levels were significantly elevated at >100 mg/kg bw/day (OECD, 2005).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Many cases of infant methaemoglobinaemia have been reported following consumption of nitrate-containing well water and vegetables with high concentrations of nitrite (see **Acute Toxicity – Observation in Humans**) (OECD, 2005).

Genotoxicity

Although all in vitro assays gave positive results with the chemical, mixed results were reported in the in vivo studies. The OECD report (2005) stated, 'the important feature of this substance for genotoxicity is the formation of nitrosamines or nitrosamides by reaction with secondary amines or amides, respectively'. However, the available data are insufficient to warrant hazard classification.

The chemical is converted to nitrous acid under acidic gastric conditions and can react with amines or amides to form carcinogenic *N*-nitroso compounds. These compounds show mutagenic activity in a variety of systems, with nitrosamines requiring metabolic activation and none required for nitrosamides (NTP, 2001; IARC, 2010). Mutagenicity was detected following combined administration of the chemical with amino compounds in animals, causing more significant activity compared to that induced by the chemical alone (NTP, 2001).

The chemical was reported to be mutagenic and clastogenic in vitro. Positive results were reported in several in vitro assays listed below (OECD, 2005):

- bacterial reverse mutation assays with strains of *Salmonella typhimurium*, with or without metabolic activation;
- reverse mutation assays with *Escherichia coli* strains with or without metabolic activation, and *Saccharomyces cerevisiae* without metabolic activation;
- induction of chromosomal aberrations and sister chromatid exchanges (SCE) in several cultured mammalian cells (Chinese hamster lung, V79-H3 and D-6 cells, Syrian hamster embryo cells, C3H mouse mammary carcinoma cells, African green monkey foetal liver cells), without metabolic activation;
- induction of SCE in human peripheral blood lymphocyte without metabolic activation;
- unscheduled DNA synthesis (UDS) in HelaS3 carcinoma cells without metabolic activation; and
- cell transformations (transformed foci type III) in mouse BALB/c3T3 cells.

Mixed results were reported with the chemical in several in vivo studies listed below (NTP, 2001; OECD, 2005; IARC, 2010):

- micronucleus formation and, 8-azaguanine- and ouabain-resistant mutations in Syrian hamster embryos in utero when pregnant females were administered the chemical (gavage) at doses up to 500 mg/kg bw, but did not induce chromosomal aberrations;
- chromosomal aberrations in the embryonic liver and bone marrow cells of pregnant rats, administered the chemical in drinking water at 210 mg/kg bw/day for 13 days;
- no increases in chromosomal aberrations in the lymphocytes of Wistar rats which received a single treatment (gavage) of 300 mg/kg bw;
- SCE induction in bone marrow cells of Swiss albino mice administered the chemical (i.p.) at 2.5–200 mg/kg bw;
- no micronucleus formation in bone marrow cells of rats and mice treated (i.p) up to 250 mg/kg bw;
- negative results in a peripheral blood micronucleus test in mice administered the chemical in drinking water up to 5000 ppm (990–1230 mg/kg bw/day);
- no increases in DNA single-strand breaks or UDS in the pyloric mucosa of F344 rats given a single oral dose of 6.9 mg/kg bw; and
- no increased UDS in early-to-mid-spermatids in mice treated with 60 and 120 mg/kg bw/day intragastrically, but sperm-head abnormality was observed 11–17 days post-treatment.

Carcinogenicity

Based on the available data, the chemical has carcinogenic potential if endogenous nitrosation occurs resulting in the formation of certain carcinogenic nitrosamines. However, the available data are insuffcient to classify the chemical as a carcinogen.

The NTP concluded that under the conditions of the study, there was *'no evidence of carcinogenic activity'* in male or female rats exposed up to 3000 ppm, *'no evidence of carcinogenic activity'* in male mice exposed up to 3000 ppm, and *'equivocal evidence of carcinogenic activity'* in female mice (NTP, 2001). The forestomach was found to be the target organ as hyperplasia occurred in rats in the two-year study and mice in the 14-week study (see **Repeat Dose Toxicity**). The World Health Organisation (WHO) concluded that there was 'no evidence of carcinogenic activity of sodium nitrite in rats and mice based on the findings of NTP carcinogenicity studies' (OECD, 2005)

The International Agency for Research on Cancer (IARC) has classified the chemical as 'probably carcinogenic to humans (Group 2A)', under conditions that result in endogenous nitrosation (IARC, 2010).

In a two year carcinogenicity study conducted by the NTP, groups of F344 rats (n = 50/sex/dose) were administered the chemical in drinking water at doses of 0, 750, 1500 or 3000 ppm (males: 0, 35, 70 or 130 mg/kg bw/day; females: 0, 40, 80 or 150 mg/kg bw/day). Both males and females showed significantly greater incidences of forestomach hyperplasia at the highest doses, compared with controls. In females, the incidence of mammary gland fibroadenoma was significantly increased at 80 mg/kg bw/day, and the incidence of multiple fibroadenoma was increased at 40 and 80 mg/kg bw/day. However, a high background incidence was observed for these neoplasms and no increase occurred at the highest dose. Significantly decreased incidences of mononuclear cell leukaemia were observed in both sexes at the mid and high dose levels. The authors concluded that under the conditions of this study, no evidence of carcinogenicity was seen at up to 3000 ppm (130–150 mg/kg bw/day) in drinking water (NTP, 2001).

In another part of this study, groups of B6C3F1 mice (n = 50/sex/dose) were administered the chemical in drinking water at the same doses as in the rat study above, equivalent to 0, 50, 120 or 220 mg/kg bw/day for males, and 0, 45, 90 or 165 mg/kg bw/day for females. In females, a positive trend in the incidences of squamous cell papilloma or carcinoma (combined) in the forestomach was observed. In males, significantly greater incidence of hyperplasia of the glandular stomach epithelium was observed at 3000 ppm (220 mg/kg bw/day) compared with the controls. Under the conditions of this study, the authors concluded that there was no evidence of carcinogenic activity in males, and equivocal evidence in females (NTP, 2001).

Nitrite is associated with the endogenous formation of *N*-nitroso compounds (see **Toxicokinetics**). Many carcinogenicity studies have been conducted in rats and mice and have shown primarily negative results. Exposure to nitrite alone in drinking water, in the diet or by gavage did not cause an increased incidence of tumours compared with the controls. In cases where carcinogenic effects were noted due to the formation of *N*-nitroso compounds when sodium nitrite was present together with specific secondary or tertiary amines or amides in the diet mix or in stomach contents. Formation of *N*-nitroso compounds can be inhibited by vitamin C and other antioxidants (NTP, 2001; OECD, 2005; IARC, 2010).

No adequate epidemiological studies for ingested sodium nitrite are available in humans. Equivocal results were reported in studies conducted to evaluate the risk for cancers following dietary intake of nitrite, or the potential for endogenous formation of *N*-nitroso compounds. Most studies report cancers in the stomach and brain, and few studies are available for other specific sites (IARC, 2010).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is considered to have low reproductive toxicity in animals. Developmental toxicity effects were considered secondary to maternal toxicity (e.g. maternal anaemia in guinea pigs increased the incidences of abortion and foetal mortality at 60 mg/kg bw/day).

In reproductive studies, the chemical did not affect reproductive parameters in pregnant Swiss CD-1 mice (when administered the chemical in drinking water up to 370 mg/kg bw/day) and in male and female rats (when administered the chemical in the diet (0.05 %) up to 43 mg/kg bw/day (NOAEL), before and during breeding) (OECD, 2005; REACH). A continuous breeding study in Swiss mice also showed no indications of reproductive or developmental toxicity up to 425 mg/kg bw/day in drinking water (NTP, 2001). However, 14-week repeated dose oral studies in rats and mice have shown fertility related effects such as testicular degeneration and reduced sperm motility at >115 mg/kg bw/day and increased oestrous lengths at >445 mg/kg bw/day (see **Repeat dose toxicity – Oral**).

Pregnant guinea pigs administered the chemical at 60 mg/kg bw/day in drinking water developed maternal anaemia, with increased incidences of abortion and foetal mortality. Subcutaneous (s.c.) injection of the chemical at 45 mg/kg bw/day during the last week of gestation caused abortion in ascorbic acid-deficient female guinea pigs (OECD, 2005).

In a developmental toxicity study, pregnant Long-Evans rats were administered the chemical in drinking water during day 0 of gestation to day 20 of lactation, at 0, 0.5, 1.0, 2.0 or 3.0 g/L (~50, 100, 200 or 300 mg/kg bw/day). The chemical severely affected erythropoietic development, growth and mortality in the offspring. No significant differences in the litters were observed between the treated and control animals. Developmental effects observed included reduced weight gain, progressively severe anaemia and mortality of the pups of dams treated at >2 g/L by the third week postpartum, and significantly changed haematological parameters (haemoglobin levels, RBC count and the mean corpuscular volumes) at >1 g/L by the second week postpartum. Cytoplasmic vacuolisation of centrilobular hepatocytes and decreased haematopoiesis in the bone marrow and spleen were also observed. The NOAEL for developmental toxicity was determined as 0.5 g/L bw/day (~50 mg/kg bw/day) (HSDB; REACH).

In a study to investigate possible embryotoxic effects, the chemical administered by oral gavage to pregnant CD-1 mice at 0.5 mg/mouse/day (~17 mg/kg bw/day) did not cause developmental effects such as foetal mortality, resorptions, changes in foetal weight or increased incidence skeletal malformations. However, foetal hepatic erythropoiesis, attributed to foetal methaemoglobinaemia was observed (OECD, 2005; REACH).

In several other studies, the chemical in drinking water at 2000 or 3000 mg/L administered to pregnant rats caused 30 % and 53 % foetal mortality, respectively. Increased foetal and pup mortality, and decreased body weights of pre-weaning pups were observed in rat dams administered the chemical in the diet at >21.5 mg/kg bw/day, but not at 10.75 mg/kg bw/day. However, oral gavage dosing on gestation day 13 at up to 120 mg/kg bw/day had no effect on dams or pups (NTP, 2001).

Other Health Effects

Neurotoxicity

In a neurotoxicity study, behavioural changes of male Long-Evans hooded rats (n = 18–24/group) were evaluated 25 minutes following administration of the chemical at 75 mg/kg bw. Severe motor incoordination was produced in animals by immersing them in water for 10 minutes before testing. No changes in metHb levels were detected. A prolonged effect of nitrite on cells in the hippocampal formation was observed (HSDB).

The chemical administered by a single subcutaneous dose of 55 mg/kg bw in three-month old male rats, suppressed their locomotor, exploratory and grooming activities. However, the effects were reversible after 24 hours. In another study, rats exposed to the chemical at 100–2000 mg/L in drinking water for two months showed changes in patterns of brain electrical activity (NTP, 2001).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation include systemic acute effects (acute toxicity from oral exposure) and eye irritation.

Under certain conditions, the chemical may form mutagenic and carcinogenic *N*-nitroso compounds.

Public Risk Characterisation

The chemical is listed on Schedules 5, 6 and 7 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP). For preparations containing more than 0.5 % of the chemical, a number of warning statements, first aid instructions and safety directions apply. These controls are considered adequate to minimise the risk to public health posed by any use in cosmetics or domestic products. The chemical is reported to be used in Australia at concentrations around 0.1 %. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

If this chemical is included in cosmetic formulations containing secondary and/or tertiary amines, mutagenic and carcinogenic *N*-nitroso compounds could be formed.

The use of this chemical in food is out of scope for this assessment. More details on using this chemical in food are available on the Food Standards Australia New Zealand (FSANZ) website (FSANZ, 2013).

Occupational Risk Characterisation

During product formulation, oral and ocular exposure may occur, particularly where manual or open processes are used. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral and ocular exposure 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 the appropriate controls.

Based on the available data, the hazard classification in the Hazardous Substances Information System (HSIS) (Safe Work Australia) is considered appropriate.

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, 2015).

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)*	Toxic if swallowed - Cat. 3 (H301)
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 the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral and ocular 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 that could 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.

The chemical should not be used in cosmetic formulations containing secondary and/or tertiary amines as it may cause the formation of mutagenic and carcinogenic *N*-nitroso compounds.

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 help meet 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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