1,2,3-Propanetriol, trinitrate: Human health tier II assessment

27 October 2017

CAS Number: 55-63-0

- Preface
- Chemical Identity
- Import, Manufacture and Use
- Restrictions
- Existing Work Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

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.

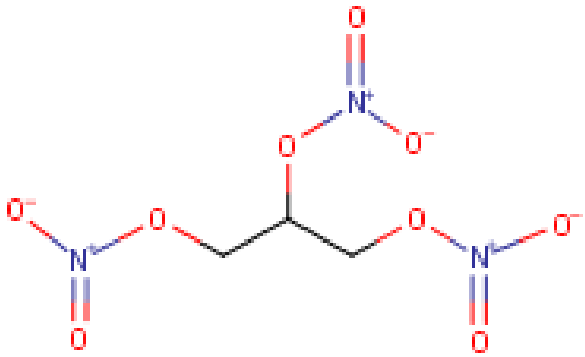
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	nitroglycerin glycerol trinitrate 1,2,3-propanetriol, trinitrate 1,2,3-propanetriyl nitrate
Structural Formula	
Molecular Formula	C3H5N3O9
Molecular Weight (g/mol)	227.09
Appearance and Odour (where available)	Colourless liquid with sweet odour
SMILES	C(CON(=O)=O)(CON(=O)=O)ON(=O)=O

Import, Manufacture and Use

Australian

The chemical has reported site-limited use, including as an explosive.

The chemical has non-industrial use as a therapeutic agent in Australia.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the Organisation for Economic Cooperation and Development (OECD) High Production Volume chemical program (HPV); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (Trainor & Jones, 1966; Midgley & Johnson, 2007)

The chemical has reported site-limited uses, including:

- in explosives;
- as a propellant; and
- in other pyrotechnical products.

The chemical has non-industrial uses, including:

- as a therapeutic agent; and
- in pesticides.

Restrictions

Australian

This chemical is listed in the *Poisons standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 3 and 4 (SUSMP, 2017).

Schedule 4

Glyceryl trinitrate except when included in Schedule 3.

Schedule 3

Glyceryl trinitrate:

a) in preparations for oral use; or

b) in preparations for rectal use.

Schedule 3 chemicals are substances, the safe use of which requires professional advice but which should be available to the public from a pharmacist without a prescription.

Schedule 4 chemicals are substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.

International

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

- EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist'); and
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Acute toxicity – category 1; H310 (Fatal in contact with skin)

Acute toxicity – category 2; H300 (Fatal if swallowed)

Acute toxicity – category 2; H330 (Fatal if inhaled)

Specific target organ toxicity (repeated exposure) – category 2; H373 (May cause damage to organs through prolonged or repeated exposure)

It also has physical hazard entries relating to its explosive properties.

Exposure Standards

Australian

No specific Australian exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit of 0.009–2 mg/m^3 (0.01–0.2 ppm) time weighted average and 0.5–2 mg/m^3 (0.05–2 ppm) short-term exposure limit in different countries such as Canada (Yukon, Quebec, British Columbia), Germany, France, Greece, Hungary, Egypt, China and Estonia.

Health Hazard Information

Nitroglycerin (NG) (CAS No. 55-63-0) is a nitrate and is used primarily as an explosive in industrial settings. It is a liquid at atmospheric conditions. The process of phlegmatisation stabilises the chemical and allows it to be formed as a solid. The solid form is commonly referred to as dynamite. The compound also has non-industrial therapeutic use as a potent vasodilator (through conversion to nitric oxide).

Toxicokinetics

Absorption

Studies show the rate of dermal absorption of NG in rats is approximately 0.85 mg/cm^2/hour. The chemical is also readily absorbed through the skin of rhesus monkeys (Wester et al.,1983).

Following intravenous administration of the chemical in rabbits and dogs at 1 mg/kg body weight (bw), the concentration of the compound in blood plasma reached its maximal level (10 µg/mL) during the first 10 to 20 minutes, with a steady and rapid decrease occurring immediately after (REACH).

Distribution

Thirty minutes following intragastric administration of radiolabelled NG, concentrations in urine and blood were 2.9 and 6.4 %, respectively (REACH).

Toxicokinetic data show that the chemical does not accumulate in organisms (REACH).

Metabolism

The biotransformation of NG consists of progressive splitting of ester bonds in the presence of reduced glutathione. The following metabolites are produced: 1,2-ethanediol dinitrate, 1,3-ethanediol dinitrate, free mononitroglycerols, glycerol and others. The chemical undergoes complete metabolism, as evidenced by the lack of NG residues in excrement in animal toxicokinetic studies (Midgley & Johnson, 2007; REACH).

Excretion

Excretion of NG metabolites occurs via the urine and exhaled breath (REACH).

Acute Toxicity

Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 2’ and hazard statement ‘Fatal if swallowed’ (H300) in the HCIS (Safe Work Australia). The available data (median lethal dose (LD50) of 685-844 mg/kg bw in rats), support this hazard classification.

The acute oral toxicity of the chemical was assessed in 2 parallel non-guideline studies. Swiss mice and Charles River CD rats of both sexes were administered a single dose of the test chemical in solution by oral gavage (the doses administered were not reported; however, effect levels were). The number of animals included in both studies was not reported, but the results suggest it was 10 males and 10 females per dose, per study. Animals were observed for a period of 14 days. Few study details were reported. Within 1 hour of dosing, all animals became cyanotic and ataxic. The ears, nose, eyes, paws and tail appeared very pale and respiration was depressed. Death occurred within 5 to 6 hours of dosing. On the basis of this study, the investigators reported oral LD50s of 1055 and 1188 mg/kg bw for female and male Swiss mice, respectively. The LD50s reported for Charles River CD rats were 884 and 822 mg/kg bw for females and males, respectively (REACH).

An acute oral toxicity study was conducted according to non-OECD, non-US EPA guidelines. Wistar rats of both sexes (5 animals per sex/dose) were administered the chemical at 159, 478, 1593 and 4779 mg/kg bw, via oral gavage. All 5 females in the highest dose group died on day 1 of the study, 4 females in the second highest dose group died on day 1 and 1 female died

from this group on day 2. Limited experimental details were provided. At necropsy, animals had signs of gastrointestinal irritation at all dose levels. Investigators reported an oral LD50 of 685 mg/kg bw on the basis of these findings (REACH).

Dermal

The chemical is classified as hazardous with hazard category 'Acute Toxicity Category 1' and hazard statement 'Fatal in contact with skin' (H310) in the HCIS (Safe Work Australia). The available data do not support this classification and it is recommended that the hazard classification be removed.

The acute dermal toxicity of NG was assessed according to the OECD Test Guideline (TG) 402 (acute dermal toxicity). Wistar rats of both sexes (10 animals/sex) were topically-administered the chemical at 9560 mg/kg bw (animals were dosed in 3 equal volume applications separated by a 30 minute absorption period). Some animals exhibited hydronephrosis and chromodacryorrhea. No significant clinical signs were observed in any animals. Under these test conditions, the test chemical did not possess acute toxicity when applied to the skin of animals. The dermal LD50 was therefore >9560 mg/kg bw (REACH).

Nitroglycerin was a very mild skin irritant in rabbits (Midgley & Johnson, 2007). No other reliable dermal LD50 values have been identified in experimental animals (NIOSH, 2011).

Inhalation

The chemical is classified as hazardous with hazard category 'Acute Toxicity Category 2' and hazard statement 'Fatal if inhaled' (H330) in the HCIS (Safe Work Australia). There are no animal data available. Data from humans are provided in the following section (see **Acute Toxicity — Observations in Humans** section). There are insufficient data to warrant removing or downgrading the existing classification.

Observation in humans

The most common and prominent manifestations of NG toxicity in humans are severe headaches and adverse cardiovascular effects (Midgley & Johnson, 2007).

Severe intoxication has been observed in humans following oral ingestion of 24 mg of the chemical, whereas doses up to 1200 mg have been tolerated with minimal effects (Windholz et al., 1976). Fatalities have occurred following reported ingestion of 2000 mg of NG (IPCS, 1990).

Due to the antihypertensive action of the chemical, patients who are already hypotensive do not tolerate the chemical well, with oral doses as low as 0.24 mg producing nausea, vomiting and syncope (IPCS, 1990).

Following inhalational exposure to the chemical at 0.4 to 0.67 mg/m^3 for 25 minutes, workers developed headaches and low blood pressure (Trainor & Jones, 1966).

It has also been reported that inhalation of nitroglycerin (phlegmatised) dust may cause toxic effects, including: nausea, vomiting, abdominal cramps, headache, confusion, delirium, bradypnoea, bradycardia, paralysis, seizures, cyanosis, methaemoglobinaemia, circulatory collapse and death (HSDB).

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate skin in animal studies. The effects were not sufficient to warrant hazard classification.

A dermal irritation study was conducted according to a US Code of Federal Regulations guideline study (Title 21). Shaved intact skin of 6 New Zealand White (NZW) rabbits (sex not specified) was exposed to the chemical at a calculated concentration of

9.72 %. The skin was assessed for evidence of irritation at 24 and 72 hours after exposure. Very few study details were reported (including exposure length, skin patch type and description of irritation). Investigators reported an overall mean irritation score of 0.46, using a scoring system where the compounds with a score >0.2 compared with controls is a mild irritant; >2.5 is a moderate irritant and >5.0 indicated severe irritation. The chemical was determined to be slightly irritating (REACH).

A dermal irritation study was conducted according to a US Code of Federal Regulations guideline study (Title 21). Shaved, abraded skin of 6 female NZW rabbits was exposed to the undiluted chemical (2 mL) under semi-occlusive conditions. The animals were observed for a period of 7 days. Few experimental details were provided. One animal developed diarrhoea during the observation period. Mean erythema and oedema scores of 0–1, and maximum scores of 4 were reported and investigators concluded that the chemical was a mild skin irritant (REACH).

Eye Irritation

The chemical is reported to be a slight eye irritant in animal studies. The effects were not sufficient to warrant hazard classification.

A US Code of Federal Regulations guideline eye irritation study (Title 21) was conducted in NZW rabbits. The chemical was instilled in to the eyes of 6 animals at a concentration of 9.72 % (in lactose and peanut oil). Animals were observed for signs of irritation at 24 and 72 hours following exposure. Very limited experimental details were provided. The investigators reported that the animals showed no signs of ocular irritation (REACH).

A non-guideline study was conducted to assess the potential for NG to cause ocular irritation in NZW rabbits. Three animals were exposed for 1 minute (eyes were rinsed with water) and 3 animals were exposed for up to 7 days (without rinsing with water). Ocular assessments were made at 1, 24, 48 and 72 hours after the end of the exposure period. The only effects observed were at 1 hour post-dosing. Corneal discharge (Draize score of 1) was observed in 2/3 animals exposed (no washing) and 3/3 animals exposed (with washing). Chemosis (Draize score of 1) was observed in 1/3 animals whose eye was washed, and conjunctival redness was observed in another rabbit whose eye was washed after treatment. No miosis, mydriasis, other ocular effects, or systemic effects were observed. All effects of exposure were fully reversible after 24 hours. On the basis of these results, the chemical was determined not to be an ocular irritant (REACH).

Observation in humans

Prolonged dermal exposure to the chemical has been reported to produce skin eruptions (Windholz et al., 1976).

There are reports of humans experiencing non-specific irritant effects when exposed to NG (Ramey & Lockey, 2006).

Sensitisation

Skin Sensitisation

Human and animal data (see **Sensitisation — Observation in Humans section**) indicate that the chemical has the potential to cause skin sensitisation. Hazard classification is warranted (see **Recommendation** section).

A non-guideline skin sensitisation test was conducted to assess the potential for NG to cause skin sensitisation. Ten guinea pigs were exposed to the chemical at a concentration of 3.41 % in peanut oil, for both the induction and challenge phases of the experiment. Four of the animals developed signs consistent with sensitisation. Although very few experimental details are available, investigators indicated the chemical acted as a ‘moderate skin sensitiser’ under these conditions (REACH).

Observation in humans

The chemical was found to be a weak sensitiser in humans when tested at a concentration of 0.01 %. No further experimental details were provided (REACH).

There are reports of humans being sensitised to NG. Allergic contact dermatitis can occur following exposure to either ointment or transdermal patches containing the chemical. The majority of people sensitised to the chemical tolerate oral forms of the chemical when used as a therapeutic agent (Ramey & Lockey, 2006).

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with hazard category 'Specific Target Organ Toxicity (Repeated Exposure) Category 2' and hazard statement ‘May cause damage to organs through prolonged or repeated exposure’ (H373) in the HCIS (Safe Work Australia). While the data are not strongly supportive of this classification, there are insufficient data to warrant removal of this classification.

An oral repeated dose toxicity study was conducted similarly to OECD TG 452 (chronic toxicity studies). Beagle dogs of both sexes (6 animals per dose) were orally administered the test chemical (as capsules) at 1, 5 or 25 mg/kg bw/day, daily for 12 months. Animals were assessed for a range of clinical and haematological parameters. Animals were necropsied at the end of the study period with gross and histopathological examinations performed. The only effect that could be contributed to dosing was mild methaemoglobinaemia. After 9 months, methaemoglobinaemia was observed in half or more of all males in the 1 mg/kg bw/day group, all animals in the 5 mg/kg bw/day and in all but 1 of the 25 mg/kg bw/day group. No evidence of severe methaemoglobinaemia (such as Heinz bodies, elevated reticulocytes or anaemia) was observed. Methaemoglobin levels returned to normal in all animals in the low and middle dose groups following a thirty day recovery period. On the basis of these results, a No Observed Adverse Effect Level (NOAEL) could not be established. A Lowest Observed Adverse Effect Level (LOAEL) of 1 mg/kg bw/day was determined (REACH).

In an oral repeated dose toxicity study conducted similarly to OECD TG 452 (chronic toxicity studies), Charles River albino rats (38 males and females per dose group) were fed diets containing the chemical at 0, 0.01, 0.1 or 1 % (equivalent to 0, 3.04, 31.5 and 363 mg/kg bw/day, and 0, 3.99, 38.1 and 436 mg/kg bw/day for males and females, respectively) for 2 years. No adverse effects were observed in any of the low dose animals. Mid-dose animals exhibited decreased weight gain in the later months of the study, and some animals in this group developed mild hepatic lesions (although no details were provided on the nature of these lesions, they were reported to have potential for malignant transformation into hepatocellular carcinomas). Animals in the high dose group had decreased weight gain, behavioural effects (reduced activity and failure to groom), anaemia with compensatory reticulocytosis, elevated serum liver enzymes) and methaemoglobinaemia. After 1 year of dosing, 8 high dose rats (sex not specified) had cholangiofibrosis and some had neoplastic foci in their livers. At 2 years, all surviving high-dose rats and 6/16 middle-dose rats had enlarged and grossly abnormal livers with severe cholangiofibrosis and hepatocellular carcinomas. There were treatment-related deaths which were attributed mainly to malignancies; however, specific details were not provided. Investigators reported NOAELs of 3.04 and 3.99 mg/kg bw/day for males and females, respectively. For reproductive effects in males, investigators reported a LOAEL of 363 mg/kg bw/day an NOAEL of 31.5 mg/kg bw/day (REACH).

In a repeated dose toxicity study, Swiss Albino CD-1 mice (58 males and females/ group) were administered NG at concentrations of 0, 0.01, 0.1 or 1.0 % (w/w) in their diet (equivalent to 0, 11.1, 114.6, 1022 and 0, 9.7, 96.4, 1058 mg/kg bw/day for males and females, respectively). Animals were dosed daily for a period of 24 months. No adverse effects were observed in the low and mid-dose groups. Decreased food consumption and weight gain were observed in the high dose group. After 1 year, high-dose animals had haem-derived pigment deposits in various organs and liver dysplasia. After 2 years, lesions were observed in the livers, spleens and/or kidneys in the high dose animals and in some of the mid-dose animals. High dose animals also had reduced weight gain, decreased grooming activity and developed methaemoglobinaemia and its sequelae. Investigators reported NOAELs of 11.1 and 9.7 mg/kg bw/day in males and females, respectively. Investigators reported LOAELs of 114.6 and 96.4 mg/kg/day for males and females, respectively, on the basis of pigment deposits in the liver, spleen and/or kidneys (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic. Some in vitro genotoxicity tests were positive, but an OECD guideline in vivo test was negative.

In vitro

The chemical was assessed for genotoxicity in an Ames test conducted similarly to OECD TG 471 (reverse bacterial mutation assay). The chemical was assessed in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, at concentrations of 5, 16.6, 50, 100, 166, 200, 333, 500, 750 or 1000 µg/plate, in the presence of absence of metabolic activation. The chemical produced statistically significant increases in the number of spontaneous revertant colonies per plate in *S. typhimurium* TA 1535, at 166 and 500 µg/plate, in the presence of metabolic activation. The chemical was negative in all other strains tested, at all concentrations (REACH).

The results from the above study were reproduced in a practically identical Ames test, conducted according to OECD TG 471. The same strains of *S. typhimurium* (TA 98, TA 100, TA 1535, TA 1537 and TA 1538) were incubated with the chemical at 15, 50, 150, 200, 500, 1500 or 2000 µg/plate, in the absence or presence of metabolic activation. The chemical was genotoxic to the TA 1535 strain, when incubated with the chemical at 500 and 1500 µg/plate in the presence of metabolic activation (REACH).

In an Ames test conducted similarly to OECD TG 471, the chemical was incubated with *S. typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100, at 10, 100, 300 and 1000 µg/plate, both in the presence and absence of metabolic activation. The chemical was negative for genotoxicity in all strains assessed; however, the investigators reported ‘weak’ mutagenic activity in the TA 1535 and 1537 strains, at the 1000 µg/plate dose in the presence of metabolic activation (REACH).

A study was performed similarly to OECD TG 476 (in vitro mammalian cell gene mutation test). Chinese hamster ovary epithelial cells were incubated with the test chemical at 50 and 144.8 µg/mL, without metabolic activation. No evidence of genotoxicity was reported in this study (REACH).

In vivo

The chemical was assessed for evidence of genotoxicity in a study conducted according to OECD TG 475 (mammalian bone marrow chromosome aberration test). Male and female CD rats (32 animals/dose) were administered the chemical at 59 or 229 mg/kg bw/day in their feed, for 4 or 13 weeks. Animals were euthanised and kidney cell cultures were established. Chromosomes were counted and morphological examination of aberrations was conducted. Investigators reported that there was no evidence of genotoxicity at either of the doses assessed. On the basis of this result, the chemical was determined not to be genotoxic (REACH).

Carcinogenicity

No guideline carcinogenesis studies have been conducted on the chemical. However, data from repeated dose toxicity studies has provided information on the carcinogenic potential of the chemical. The International Agency for Research on Cancer (IARC) classifies nitrates and nitrites as 'probably carcinogenic to humans' (Group 2A) under certain conditions (i.e. ingested nitrate or nitrite under conditions that result in endogenous nitrosation) which could lead to the formation of known carcinogens such as N-nitroso compounds (IARC, 2010). The evidence below supports classification of NG as a carcinogen (see **Recommendation** section).

In an oral repeated dose toxicity study conducted similarly to OECD TG 452 (chronic toxicity studies), Charles River CD albino rats (38 males and females per dose group) were fed diets containing the chemical at 0, 0.01, 0.1 or 1 % (equivalent to 0, 3.04, 31.5 and 363 mg/kg bw/day, and 0, 3.99, 38.1 and 436 mg/kg bw/day for males and females, respectively) for 2 years (see **Repeated Dose Toxicity** section). After 1 year of dosing, 8 high dose rats (sex not specified) had cholangiofibrosis and some had neoplastic foci in their livers. At 2 years, all surviving high-dose rats and 6/16 middle-dose rats had enlarged and grossly abnormal livers with severe cholangiofibrosis and hepatocellular carcinomas. Some of these animals had secondary malignant

neoplasms in the lungs. Testicular interstitial tumours were also observed in half of the high dose males, leading to impaired spermatogenesis in some. There was also an increase in the incidence of chromophobic pituitary adenomas (a naturally occurring tumour in Charles River rats), and mammary tumours in females. There were treatment-related deaths which were attributed mainly to malignancies; however, specific details were not provided. Investigators reported NOAELs of 3.04 and 3.99 mg/kg bw/day for males and females, respectively (REACH).

In a repeated dose toxicity study, Swiss Albino CD-1 mice (58 males and females/group) were administered NG at concentrations of 0, 0.01, 0.1 or 1.0 % (w/w) in feed (equivalent to 0, 11.1, 114.6, 1022 and 0, 9.7, 96.4, 1058 mg/kg bw/day for males and females, respectively). Animals were dosed daily for a period of 24 months (see **Repeated Dose Toxicity** section). After 1 year, high-dose animals had haem-derived pigment deposits in various organs and liver dysplasia. After 2 years, lesions were observed in the livers, spleens and/or kidneys in the high dose animals and in some of the mid-dose animals. No further analysis of the nature of the lesions was provided. Investigators reported NOAELs of 11.1 and 9.7 mg/kg bw/day in males and females, respectively. Investigators reported LOAELs of 114.6 and 96.4 mg/kg/day for males and females, respectively, on the basis of pigment deposits in the liver, spleen and/or kidneys (REACH).

Reproductive and Developmental Toxicity

Based on the available data, the chemical may present a risk of developmental and reproductive toxicity. Hazard classification is warranted (see **Reconmmendation** section).

A 3-generation reproductive study was conducted similar to OECD TG 416 (2−generation reproduction toxicity study) in CD rats, where the parental generation (F0) received NG in their feed at 0, 0.01, 0.1 or 1 % for 6 months prior to mating (equivalent to 0, 3.6, 39.0 or 408, and 0, 5.0, 46.0 or 452 mg/kg bw/day, for males and females respectively). Matings consisted of 10 males and 20 females from each dose group for the F0 generation. Twenty to 24 pups from the 2nd litters were randomly chosen in equal numbers from each treatment group and maintained at each respective treatment level. At 3 months of age, each male was mated with a female from each group and again, only the 2nd generation offspring were selected for continued treatment. This was repeated until the animals from the 3rd generation (F3b's) were weaned. Fertility in the F1 and F2 generation of high-dose males was severely impacted. These effects appeared to result from the decreased feed intake and consequent poor nutritional status of the females and decreased spermatogenesis (due to interstitial tumours) in the males. The F2a males were impotent, with an average reduction in their teste size of 25 %. No other developmental or reproductive effects were identified. Investigators reported No Observed Effect Levels (NOEL) of 39 mg/kg bw/day and 46 mg/kg bw/day in the F1a generations for males and females, respectively (Midgley & Johnson, 2007; REACH).

A developmental toxicity study was conducted according to US FDA guidelines. Mature female CD rats were mated with young adult male rats. The dams were dosed with the chemical in their diet, on gestation days (GD) 6–15, and sacrificed on GD 20. There were 3 dose groups and doses were calculated retrospectively, but not specifically reported. Dams and foetuses were assessed for a range of parameters. Significant reduction in the weights of high dose females was seen at the end of the study. Liver-to-body weight ratios were significantly increased in the high dose group. Offspring of the high dose animals exhibited diaphragmatic hernias which were reported to be a result of exposure to the test chemical; however, the increased incidence was not statistically significant. The incidence of unossified (or incompletely ossified) hyoid bones was significantly increased in the high dose offspring. An NOEL of 6.4 mg/kg bw/day was determined on the basis of teratogenicity (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, reproductive and developmental toxicity), systemic acute effects (acute toxicity from oral/inhalation exposure) and local effects (skin sensitisation). The chemicals can also cause harmful effects following repeated exposure.

While the chemical causes repeated dose toxicity via the oral route at very high doses, the doses at which there is a risk for carcinogenesis are lower.

Public Risk Characterisation

Given the industrial uses identified for the chemical, it is unlikely that the public will be exposed from industrial sources. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical (systemic long-term, systemic acute and local) health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **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, 2017).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of environmental or physicochemical hazards. These are outside the scope of this assessment and any existing HCIS classifications in those categories are not recommended to be changed.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Fatal if swallowed - Cat. 2 (H300)* Fatal if inhaled - Cat. 2 (H330)*
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)*

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Not Applicable	Suspected of causing cancer - Cat. 2 (H351)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility or the unborn child - Cat. 2 (H361)

[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, dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures 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.

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.

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