Picramic acid and sodium picramate: Human health tier II assessment

08 March 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, 2-amino-4,6-dinitro-	96-91-3
Phenol, 2-amino-4,6-dinitro-, monosodium salt	831-52-7

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

Grouping Rationale

The chemicals in this group consist of a substituted phenolic compound, picramic acid (CAS No. 96-91-3) and its sodium salt, sodium picramate (CAS No. 831-52-7). As the toxicokinetics and toxicity of these chemicals are expected to be similar, they are grouped together for purposes of human health risk assessment. While there may be differences between the free acid and the sodium salt with respect to the local effects, the speciation of the chemicals in biological fluids will be dependent on pH but independent of the original chemical form.

Import, Manufacture and Use

Australian

The chemicals in this group have been reported to be used in hair dyes in Australia (NICNAS, 2007).

International

The following international uses have been identified through the European Chemicals Agency (ECHA) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database; eChemPortal; Galleria Chemica; Health Canada Cosmetic Ingredient Hotlist; New Zealand Inventory of Chemicals (NZIoC); Substances and Preparations in the Nordic countries (SPIN) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the US Department of Health and Human Services Household Products Database (US HPD).

The chemicals in this group are used in cosmetics as colourants or dyes in hair dye products up to a maximum concentration of 0.6 % (CIR, 2009; SCCS, 2012; HSDB). Sodium picramate is a non-reactive dye that is used as a direct hair colouring agent (imparts temporary colour by coating the outer layer of hair) in both non-oxidative and oxidative hair dye formulations (SCCS, 2012). Since hair dye formulations are generally alkaline in nature, picramic acid will always exist in its basic form as picramate in typical hair dye products (CIR, 2009; SCCS, 2012) and is likely to be used in the same way as sodium picramate in hair dyes. In the US, picramic acid and sodium picramate were reported to be used in 5 and 31 hair dye products, respectively (CIR, 2009). The chemicals are restricted for use in cosmetics in a number of countries (see **Restrictions: International** section).

The following commercial uses have been reported for the chemicals in this group (CIR, 2009; Galleria; HSDB; REACH; REACHa):

- in the manufacture of dye intermediates (including azo dyes) and other organic compounds; and
- picramic acid is used for dyeing fur.

The following site-limited uses have been reported for the chemicals in this group (Galleria; HSDB; REACH; REACHa):

- sodium picramate is used in pyrotechnics (explosives) and rocket fuel.

In the EU, picramic acid and sodium picramate have a reported annual use of 0–10 tonnes and 100–1000 tonnes, respectively (REACH, REACHa).

Restrictions

Australian

No known consumer use restrictions have been identified.

The industrial (non-consumer) use, storage and transport restrictions include the following—picramic acid is classified as explosive (division 1.1) in the Hazardous Chemical Information System (HCIS), and is subject to regulations set in the Explosives Act 2003 administered by Safe Work Australia (Safe Work Australia).

International

The use of the chemicals in this group in hair dye products is restricted by the EU and the Association of Southeast Asian Nations (ASEAN) as ‘substance which cosmetic products must not contain except subject to restrictions laid down’ in the following (ASEAN Cosmetic Directive; CosIng; Galleria Chemica):

- EU Council Directive 2012/21/EU—No. 1197/2013 Annex III/280; and
- ASEAN Cosmetic Directive Annex III.

The restrictions in the EU and ASEAN for use as hair dyes in oxidative hair dye products include:

- after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 0.6 %; and
- to be printed on the label: the mixing ratio; and “ Hair colorants can cause severe allergic reactions. Read and follow instructions. This product is not intended for use on persons under the age of 16. Temporary ‘black henna’ tattoos may increase your risk of allergy. Do not colour your hair if:—you have a rash on your face or sensitive, irritated and damaged scalp,—you have ever experienced any reaction after colouring your hair,—you have experienced a reaction to a temporary ‘black henna’ tattoo in the past.”

The restrictions in the EU and ASEAN for use as hair dyes in non-oxidative hair dye products include:

- maximum concentration in finished cosmetic products is 0.6 %.

The ASEAN Directive has the following additional restrictions:

- use for dyeing eyelashes and eyebrows is not permitted; and
- the direction for use “wear suitable gloves” must be included in label or leaflet text.

Sodium picramate is restricted for use in cosmetic products in Canada, with a maximum permitted concentration of 0.1 % (Health Canada).

No specific restrictions for the chemicals were identified from the New Zealand Inventory of Chemicals (NZIoC).

Existing Worker Health and Safety Controls

Hazard Classification

Picramic acid is classified as hazardous, with the following hazard categories and hazard statements for human health in the HCIS (Safe Work Australia):

Acute toxicity—Category 4; H302 (Harmful if swallowed);

Acute toxicity—Category 4; H312 (Harmful in contact with skin); and

Acute toxicity—Category 4; H332 (Harmful if inhaled).

Sodium picramate is not listed on the HCIS.

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

Based on available data, the chemicals in this group are expected to be poorly absorbed through skin when used in hair dye products.

In a guideline study (Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 428), in vitro dermal absorption of sodium picramate (corresponding to 1.25 % active ingredient) in a 'standard formulation' containing hydrogen peroxide was evaluated in dermatomed pig skin (CIR, 2009; SCCS, 2012). The chemical distribution was analysed 24 hours following a 30 minute exposure period and reported (as % of applied dose) as follows:

- receptor fluid—0.67 ± 0.68 % (0.38 ± 0.37 µg/cm^2);
- stratum corneum (isolated by tape stripping)—0.23 ± 0.11 % (0.14 ± 0.06 µg/cm^2);
- epidermis and upper dermis—0.00 ± 0.00 % (0.00 ± 0.00 µg/cm^2); and
- washing solution—96.31 ± 7.98 % (59.04 ± 13.34 µg/cm^2).

The total absorption (receptor fluid + epidermis + upper dermis) was reported to be 0.67 ± 0.68 % (0.38 ± 0.37 µg/cm^2). Due to the high variability in data, the mean + 2 SD (standard deviation), equating to a total absorption of 2 % or 1.12 µg/cm^2, was used for calculating the margin of safety (MOS) under oxidative conditions (SCCS, 2012) (see **Public risk characterisation** section).

An in vivo study in rats conducted similarly to OECD TG 427 showed that while radiolabelled picramic acid in a penetration enhancing solvent (dimethyl sulfoxide, DMSO) was well absorbed (up to 25 %) through the skin, the chemical in a typical hair dye formulation was poorly absorbed (less than 5 %) (CIR, 2009; REACHa). Within 72 hours after application, 18 % of the chemical in DMSO and 0.4 % of the chemical in hair dye formulation were eliminated from the body. Excretion was both in urine and faeces to similar extents. The remainder of the chemical was retained within the body, in both cases, the greatest mean concentrations of radioactivity were found in the liver, kidneys, adrenal and thyroids in both sexes.

Acute Toxicity

Oral

Picramic acid is classified as hazardous with the hazard statement 'Harmful if swallowed' (H302) in the HCIS (Safe Work Australia). However, the median lethal dose (LD50) of 110 mg/kg bw in rats for picramic acid warrants an amendment of the existing classification. The same hazard classification will also apply to sodium picramate (see **Recommendation** section).

A non-guideline acute oral toxicity study in rats reported an LD50 of 110 mg/kg bw for picramic acid (CIR, 2009; SCCS, 2012; REACH). The animals (n=5/sex/group) were dosed at 0, 100, 160, 250, 400 or 640 mg/kg bw by gavage. Treatment-related adverse effects such as lethargy, piloerection and orange staining of external extremities were seen shortly after dosing. These signs were followed by gasping in six animals dosed at 100 mg/kg bw. They died within 1–19 hours of treatment. The LD50 and its 95 % confidence limits were calculated to be 110 (63–176) mg/kg bw.

A non-guideline study reported an LD50 of 378 mg/kg bw for picramic acid in mice (CIR, 2009; REACHa; RTECS).

Dermal

Picramic acid is classified as hazardous with the hazard statement 'Harmful in contact with skin' (H312) in the HCIS (Safe Work Australia). While no animal data are available, occupational exposure data show that the chemicals in this group may cause acute poisoning justifying the retention of the hazard classification. The same classification will also apply to sodium picramate (see **Recommendation** section).

Acute toxicity of the chemicals in this group in humans is reported to be similar to that of 2,4 dinitrophenol (CAS No. 51-28-5), which causes severe occupational poisoning upon dermal exposure (Haz-map; Merck index) (see **Acute toxicity: Observation in humans** section).

Inhalation

Picramic acid is classified as hazardous with the hazard statement 'Harmful if inhaled' (H332) in the HCIS (Safe Work Australia). While no animal data are available, occupational exposure data show that the chemicals in this group may cause acute poisoning justifying the retention of the hazard classification. The same classification will also apply to the sodium salt (see **Recommendation** section).

The acute toxicity of the chemicals in this group is reported to be similar to that of 2,4 dinitrophenol (CAS No. 51-28-5), which causes occupational poisoning upon inhalation of the liquid spray (Haz-map; Merck index) (see **Acute toxicity: Observation in humans** section).

Observation in humans

Occupational exposure to the chemicals in this group may occur through inhalation and dermal contact at workplaces where these chemicals are produced or used (HSDB). Symptoms of acute poisoning are reported to be similar to that of 2,4 dinitrophenol (CAS No. 51-28-5), which include fatigue, profuse sweating, flushing of face, dizziness, abdominal cramps, nausea, vomiting, bloody diarrhoea, weakness, and occasionally leading to convulsions, loss of consciousness and death (HSDB).

Corrosion / Irritation

Skin Irritation

Based on available data, the chemicals in this group are not expected to be irritating to skin.

In a non-guideline study, picramic acid was not irritating to rabbit skin (intact or abraded) when applied to 3 animals as an aqueous solution at 2.5 % under an occlusive patch for 24 hours (CIR, 2009; SCCS, 2012; REACH).

Eye Irritation

The chemicals in this group are mildly irritating to eyes, however, data are not sufficient to support classification.

In a non-guideline study in rabbits (n=3), picramic acid was reported to be irritating to eyes (SCCS 2012; REACH). The chemical was applied to one eye of each animal as an aqueous solution at 2.5 % (buffered to pH 7) for 10 seconds and rinsed off. Conjunctival redness was seen in all treated eyes for up to 4 days, and persisting to 7 days in one animal (scores unavailable).

In a similar study in albino rabbits, sodium picramate/ picramic acid at 2.5 % in aqueous solution (pH 7) caused mild conjunctival inflammation in all 3 animals for up to 72 hours post-application (scores unavailable) (CIR 2009; REACHa).

Sensitisation

Skin Sensitisation

Based on available data, the chemicals in this group are considered to be sensitising to skin, warranting hazard classification (see **Recommendation** section).

In a local lymph node assay (OECD TG 429), sodium picramate in DMSO was found to be a moderate skin sensitiser (CIR, 2009; SCCS, 2012; REACHa). The following stimulation indexes (SI) were produced at the respective test concentrations—1.2 (1 %), 2.7 (5 %), 3.6 (10

%), 7.0 (25 %) and 11.4 (50 %). The estimated concentration needed to produce a threefold increase in lymphocyte proliferation (EC3) was determined to be 6.7 %.

In an open epicutaneous test (OET) performed with a multiple dose regime for induction and challenge, picramic acid was reported to be a mild sensitiser at 0.2 % (in distilled water) producing a positive dermal response in 4/15 guinea pigs, 24 hours after challenge (Kimber et al., 2001; CIR, 2009; REACH). Pre-sensitised female albino guinea pigs were exposed to the chemical at 0.002 %, 0.02 % and 0.2 % (in distilled water) in both induction and challenge phases. The dermal response consisted of slight erythema (redness) (Draize score=1), which was resolved within 48 hours of challenge. Slight erythema was also observed during induction.

Repeated Dose Toxicity

Oral

Data available indicate that the chemicals in this group may induce gastrointestinal damage following repeated oral exposure; however, there is lack of consistency and severity of the effects. The chemicals may cause testicular damage following repeated oral exposure as discussed in the **Reproductive and developmental toxicity** section.

In a 90-day oral toxicity study (OECD TG 408), specific-pathogen-free (SPF) rats (n=10/sex/group) were dosed daily for 13 weeks with 0, 5, 15 or 80 mg/kg bw/day sodium picramate (purity 62.4 %) by gavage (CIR, 2009; SCCS, 2012; REACH; REACHa). There were no deaths in any of the dose groups. Significant treatment-related adverse effects were observed from 15 mg/kg bw/day (in females) and at 80 mg/kg bw/day (in males) and they included the following:

- macroscopic lesions on the stomach, caecum and/or mesenteric lymph nodes in some of the animals of both sexes (number of animals affected was not reported). Cell damage in the gastrointestinal tract included ulceration, inflammation and fibrosis. These effects persisted to the end of the 4-week recovery period;
- macroscopic lesions in the liver and kidneys in both sexes, and in adrenals in male rats. These were reversed by the end of the recovery period;
- haematotoxicity—signs included slightly increased mean corpuscular volume and mean corpuscular haemoglobin, increased number and maturity index of reticulocytes (immature red blood cells), and moderately increased number of white blood cells (including neutrophils, monocytes and lymphocytes). There was evidence of increased haemopoiesis (formation of blood cells) in the bone marrow and spleen. All these effects were reversed by the end of the recovery period;
- increase in absolute and relative liver, kidney and spleen weights, which were reversed by the end of the recovery period; and
- clinical parameters indicating changes in metabolism were observed only in the highest dose group in both sexes. No significant changes were seen in the physical, ophthalmic or urine analysis parameters.

Based on these effects, a no observed adverse effect level (NOAEL) of 5 mg/kg bw/day (corresponding to 3.1 mg/kg bw/day active ingredient) was determined for sodium picramate.

In the accompanying 14-day range-finding study (OECD TG 407) (n=5/sex/group), significant gastrointestinal toxicity was seen at 250 mg/kg bw/day (the highest dose tested), but not at lower doses (20 and 100 mg/kg bw/day) (SCCS, 2012). Deaths (2 males and 3 females) were observed only at 250 mg/kg bw/day. The treatment-related adverse effects seen in both sexes (1–3 animals/sex) included enlarged spleen, thickened caecum, and changes in the colon such as foci, nodules or thickened colon (also seen in 1 female at 100 mg/kg bw/day); and reduced testes, epididymis, prostate and seminal vesicles in 3 males.

Dermal

There is insufficient evidence to determine the health effects of the chemicals following repeated dermal exposure.

In a 90-day non-guideline dermal study in rabbits, an oxidative hair dye formulation containing sodium picramate at 0.1 % did not cause any significant adverse effects (CIR, 2009; REACH; REACHa). The hair dye formation was applied to clipped rabbit skin (n=6/sex) for 1 hour per treatment and then washed thoroughly. Treatment consisted of two applications per week for 13 weeks. Slight thickening of skin was seen at the application sites. No significant changes were reported in blood or urine analysis.

Inhalation

No data are available.

Genotoxicity

The chemicals in this group are not considered to be genotoxic based on weight of evidence from available data.

The following in vitro data are available (CIR, 2009; SCCS, 2012; REACH; REACHa):

- Both the chemicals in this group tested positive for gene mutations in bacteria. Sodium picramate was mutagenic in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA98 with metabolic activation but not in strains TA100, TA102, TA1535 and TA1537, both with and without metabolic activation (at 3-5000 µg/plate). In two separate Ames tests, picramic acid was found to be mutagenic in all strains of *S. typhimurium* tested including TA98, TA100, TA1535, TA1537 and TA1538, with and without metabolic activation (from 0.5 up to 1000 µg/plate).
- Both the chemicals in this group tested negative for gene mutations in separate mouse lymphoma assays at the thymidine kinase (tk) locus at the following concentrations: a) sodium picramate (OECD TG 476)—at 112-1200 µg/mL and 28-450 µg/mL with and without metabolic activation, respectively; and b) picramic acid—at 15-150 µg/mL and 30-240 µg/mL with and without metabolic activation, respectively.
- Picramic acid was not genotoxic in a chromosomal aberration test (OECD TG 473) in Chinese hamster ovary cells (CHO) at 0.5-1250 µg/mL, with and without metabolic activation.
- Picramic acid tested negative in a sister chromatid exchange assay in mouse lymphoma cells at 0.6-20 µg/mL, with and without metabolic activation.

The following in vivo data are available (CIR, 2009; SCCS, 2012; REACH):

- Picramic acid was not genotoxic in an in vivo mammalian erythrocyte micronucleus test (OECD TG 474). The chemical did not induce an increase in micronucleated polychromatic erythrocytes (indicating a non-interference with chromosomal structure or distribution) in the bone marrow cells of mice dosed at 50 mg/kg bw/day.
- Sodium picramate was not genotoxic in an in vivo unscheduled DNA synthesis (UDS) test (OECD TG 486). The chemical did not induce DNA damage leading to increased (unscheduled) repair synthesis in hepatocytes of rats dosed up to 110 mg/kg bw/day.

Carcinogenicity

Carcinogenicity of the chemicals in this group cannot be inferred from the limited data available.

In a non-guideline study, dermal application of an oxidative hair dye formulation containing 0.01 % picramic acid once per week for 20 months produced no significant increases in tumours in Swiss mice (n=60/sex) relative to control group (Jacobs et al., 1984; CIR, 2009).

Reproductive and Developmental Toxicity

Based on available data, the chemicals in this group are not expected to have specific developmental toxicity. However, data indicate that the chemicals may induce testicular damage on repeated oral exposure at 80 mg/kg bw/day, warranting hazard classification for specific reproductive toxicity.

In a 90-day oral toxicity study (OECD TG 408), testicular toxicity was seen in male SPF rats dosed daily by gavage with sodium picramate at 80 mg/kg bw/day for 13 weeks (see **Repeated dose toxicity: Oral** section). Cellular damage (and reduced organ weight) was seen in the testes and epididymis in 9 out of 10 male rats dosed at 80 mg/kg bw. Signs of cellular damage included severe tubular degeneration, sperm granuloma, azoospermia, and oligospermia. These effects persisted to the end of the 4-week recovery period. The prostate and seminal vesicles were not affected. In the accompanying 14-day range-finding study (OECD TG 407) (n=5/sex/group), reduced testes, epididymis, prostate and seminal vesicles was seen in 3 animals at the highest dose of 250 mg/kg bw/day, but not at lower doses (20 and 100 mg/kg bw/day).

In a prenatal development study (OECD TG 414), picramic acid produced no significant toxicity in female rats, when dosed at 0, 10, 30 or 60 mg/kg bw/day by gavage on gestation days 5–15 (CIR, 2009; SCCS, 2012; REACH). Apart from an increase in foetal body weight (and uteri weights) seen in the highest dose group, foetal development was not adversely effected by the treatment. Maternal and foetal NOAELs of 30 mg/kg bw/day were determined for the chemical.

In a non-guideline teratogenicity study, topical application of an oxidative hair dye formulation containing 0.1 % sodium picramate, every third day during gestation days 1–19 produced no embryonic or teratogenic effects in CD rats (n=20) (CIR, 2009; REACHa).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the following:

- systemic long-term effects (male reproductive toxicity); and
- skin sensitisation.

The chemicals can also cause harmful effects on repeated oral exposure; and on single oral, dermal, or inhalation exposure.

Public Risk Characterisation

The chemicals in this group are reported to be used in hair dyes in Australia. The chemicals induced skin sensitisation. Induction and/or elicitation of allergic responses may occur in concentrations below those allowed in the EU.

The EU and ASEAN have restricted the use of these chemicals in hair dyes to a maximum concentration of 0.6 % (see **Restrictions: International** section). Following a safety evaluation, the Scientific Committee on Consumer Safety (SCCS) concluded that the use of these chemicals in oxidative and non-oxidative hair dye formulations at a maximum on-head concentration of 0.6 % does not pose a risk to the health of the consumer, apart from sensitising potential (SCCS, 2012). A sensitisation warning is mandated in the EU at any concentration.

A margin of safety (MOS) of 155 was derived from dermal absorption (see **Toxicokinetics** section) and NOAEL from the 90-day oral toxicity study (see **Repeated dose toxicity: Oral** section). The MOS based on haematotoxicity, microscopic findings in the gastrointestinal tract, and macroscopic findings in the liver and kidney is also of concern being close to the value (MOS of 100) of what is generally considered safe for use (SCCS, 2016).

Currently, there are no restrictions on the use of these chemicals in cosmetics in Australia. In the absence of any regulatory controls, the characterised critical health effects, particularly skin sensitisation, have the potential to pose an unreasonable risk to the public when used in hair dyes. The risk could be mitigated by implementing restrictions for the use of the chemical in hair dyes.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, acute and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. The chemicals 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.

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

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health from the potential use of the chemicals in hair dyes be managed through changes to the *Poisons Standard*, and risks for workplace health and safety be managed through classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that the chemical be included in the *Poisons Standard—The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) for use in hair dyes, to ensure appropriate restrictions and labelling.

Consideration should be given to the following:

- the chemicals cause systemic acute effects (acute toxicity from oral, dermal and inhalation exposures)
- the chemicals are skin sensitisers;
- they may induce male reproductive toxicity;
- the low NOAEL from the 90-day oral toxicity study of 5 mg/kg bw/day and the observed toxic effects, indicating that the chemicals can cause harmful effects on repeated oral exposure at low concentrations (see **Repeated dose toxicity: Oral** section);
- the margin of safety (MOS) derived from the dermal absorption (see **Toxicokinetics** section) and NOAEL from the 90-day oral toxicity study is 155. It is very close to the safe threshold of 100, which is generally recommended for cosmetic ingredients (SCCS, 2016);
- overseas restrictions for use of these chemicals in hair dyes. The maximum authorised concentration in cosmetics as colourants or dyes in hair dye products is 0.6 % (see **International Restrictions** section); and
- a sensitisation warning is mandated in the EU at any concentration.

Work Health and Safety

The chemicals are 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 physical hazards and environmental hazards.

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	Toxic if swallowed - Cat. 3 (H301) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (H317)
Reproductive and Developmental Toxicity	Not Applicable	May damage fertility - Cat. 1B (H360F)

[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 chemicals 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 chemicals 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 chemicals are 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 chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

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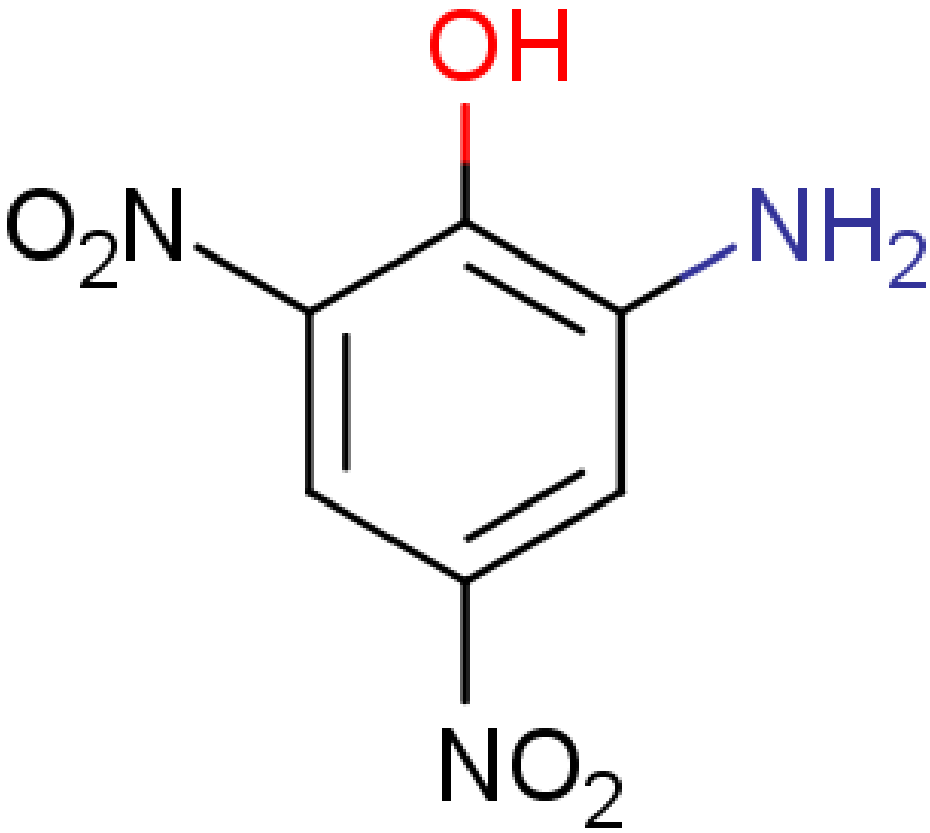
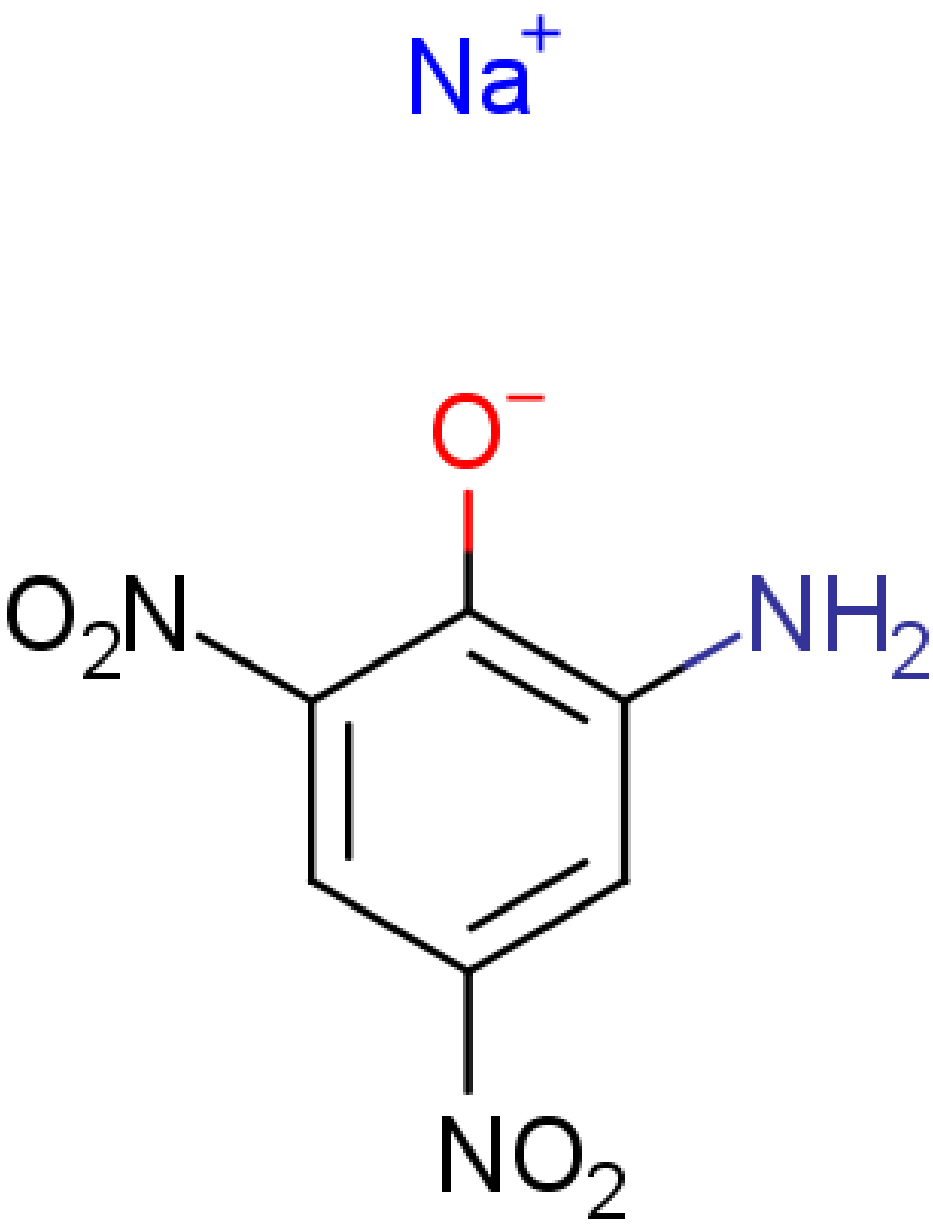
Last Update 08 March 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, 2-amino-4,6-dinitro-** picramic acid 2-amino-4,6-dinitrophenol
CAS Number	96-91-3
Structural Formula	

	
Molecular Formula	C6H5N3O5
Molecular Weight	199.12

Chemical Name in the Inventory and Synonyms	**Phenol, 2-amino-4,6-dinitro-, monosodium salt** sodium picramate sodium 2-amino-4,6-dinitrophenoxide 2-amino-4,6-dinitrophenol, sodium salt
CAS Number	831-52-7
Structural Formula	

	
Molecular Formula	C6H5N3O5.Na
Molecular Weight	221.10

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