Phenol, 3-nitro-: Human health tier II assessment

28 June 2019

CAS Number: 554-84-7

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.

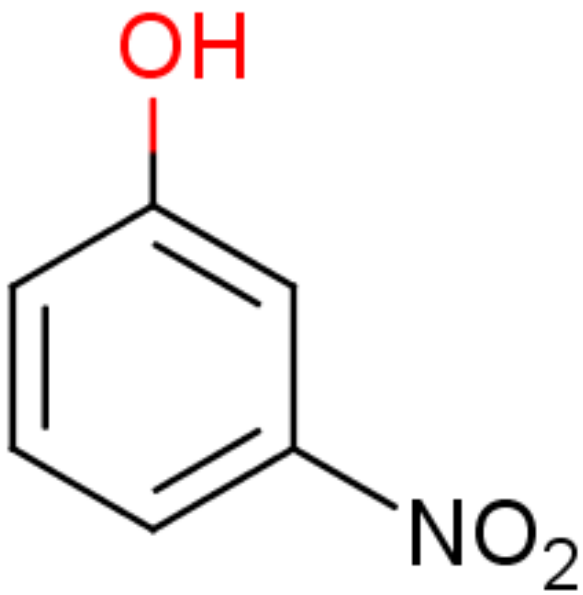
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	3-nitrophenol m-nitrophenol m-hydroxynitrobenzene
Structural Formula	
Molecular Formula	C6H5NO3
Molecular Weight (g/mol)	139.11
Appearance and Odour (where available)	Colourless to pale yellow crystalline solid
SMILES	c1(O)cc(N(=O)=O)ccc1

Import, Manufacture and Use

Australian

The chemical is not included in the list of chemicals used in permanent and semi-permanent hair dyes in Australia (NICNAS, 2007). No other use, import, or manufacturing information was available.

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; 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 Information on Hazardous Chemicals and Occupational Diseases (Haz-Map); the US Department of Health and Human Services Household Products Database (US HPD) and the US National Toxicology Program (NTP).

The chemical has reported cosmetic use in hair dyeing or as a hair colourant (CosIng; INCI). However, there is currently no documented use of the chemical in cosmetic products (Personal Care Products Council, 2011; CosIng; Environmental Working Group (EWG) Skin Deep Cosmetics Database; US HPD).

The chemical has reported commercial uses, including as:

- a fungicide for leather and leather products; and
- an additive in tobacco products.

The chemical has reported site-limited uses, including:

- in the synthesis of dye intermediates, chemicals and drugs; and
- in leather tanning and processing.

The chemical is a natural component of tobacco and can be released into the atmosphere in tobacco smoke (NTP).

Restrictions

Australian

The chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6 under the entry for NITROPHENOLS (SUSMP, 2019).

Schedule 6:

'NITROPHENOLS, ortho, meta and para, **except** when separately specified in these Schedules.'

Schedule 6 chemicals are labelled 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label (SUSMP, 2019).

International

No specific international restrictions were identified for the chemical.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards have been reported for the chemical—exposure limit of 3 mg/m³ time-weighted average (TWA) and short-term exposure limit (STEL) of 6 mg/m³ in Russia (Galleria; RTECS).

Health Hazard Information

In literature, the 3 structural isomers of nitrophenol (ortho, meta and para) are often collectively referred to as mononitrophenols or nitrophenols. It appears that the toxicity of nitrophenols as a collective group was determined primarily from the data available on the para and ortho isomers. There is limited data on the meta isomer.

Toxicokinetics

Mononitrophenols are readily absorbed into the body by ingestion, inhalation of their aerosols and through the skin (HSDBa, CICAD, 2000). Animal studies showed that all 3 structural isomers were rapidly metabolised and excreted following similar metabolic pathways of conjugation and to a lesser extent reduction (CICAD, 2000; HSDB; NTP).

Following oral administration, 80 % of the administered chemical was excreted in the urine within 24 hours in various studies in rabbits, mice and rats (CICAD, 2000; HSDB; NTP). About 68–86 % of the excreted chemical was in a conjugated form as glucuronide and/or sulfate ester; and 7–13 % was reduced to aminophenol. In rabbits, less than 1 % of the administered chemical was also found to undergo oxidation (HSDB; NTP).

In vitro studies showed that dermal absorption of the chemical occurred through simple diffusion (CICAD, 2000; HSDB). Regardless of the route of exposure, bioaccumulation is not expected as any absorbed chemical is rapidly metabolised and excreted (CICAD, 2000; HSDB).

Acute Toxicity

Oral

The chemical has moderate acute toxicity on oral exposure with a reported median lethal dose (LD50) of 328 mg/kg bw in rats, warranting hazard classification (see **Recommendation** section).

The following oral LD50 values have been reported for the chemical from various studies—rat (328 and 930 mg/kg bw), mouse (1070 mg/kg bw) and unspecified mammal species (250 mg/kg bw) (CICAD, 2000; HSDB; NTP; RTECS). No data are available on the non-lethal toxic effects of the chemical.

Dermal

Available data show that the chemical may have moderate acute dermal toxicity with a reported dermal LD50 value of 528 mg/kg bw, warranting hazard classification (see **Recommendation** section).

A dermal LD50 of 528 mg/kg bw has been reported for the chemical in unspecified mammalian test species (RTECS). No data are available on the non-lethal toxic effects of dermal exposure.

Inhalation

The limited animal data available indicate no mortality following inhalation exposure. However, due to the effects seen in humans on inhalation exposure (see **Acute toxicity: Observations in humans** section), acute inhalation toxicity of the chemical cannot be excluded.

Limited acute inhalation toxicity data are available for the chemical. One study reported that no mortality or toxic effects were seen in rats exposed to an atmosphere saturated with the test substance (mononitrophenol, isomer unspecified) at 20 °C for 8 hours.

Observation in humans

Mononitrophenols can be toxic by all routes of exposure—dermal, ocular, oral and inhalation (CICAD, 2000). Acute toxic effects may include skin burns; redness, pain and burns to the eyes; bluish discolouration of the skin; cough and sore throat, vomiting, nausea, abdominal pain, headache, dizziness, shock, convulsions, unconsciousness, and mortality from cardiac or pulmonary failure (CICAD, 2000; HSDB, HSDBa). Exposure to chemicals similar to nitrophenols can cause methaemoglobinaemia (a disorder of the blood which results in impaired oxygen transport in the body) (Blanco & Blanco, 2017; CICAD, 2000).

Corrosion / Irritation

Skin Irritation

The chemical can cause skin irritation in humans, warranting hazard classification (see **Recommendation** section). Available animal data show irritant effects following 24-hour exposure.

The chemical is irritating to human skin (CICAD, 2000; HSDB). Acute toxic effects of dermal exposure to the chemical can include skin burns (see **Acute toxicity: Observations in humans** section).

In a Draize test, the chemical (20 mg) was reported to be moderately irritating to rabbit skin 24 hours after dermal application (RTECS). No other study details were available.

Eye Irritation

The chemical can cause serious eye damage in humans, warranting hazard classification (see **Recommendation** section). Available animal data support the classification.

Acute toxic effects of ocular exposure to the chemical can include redness, pain and burns to the eyes (see **Acute toxicity: Observations in humans** section).

In a Draize test, the chemical (5 mg) was reported to be severely irritating to rabbit eyes 24 hours following direct instillation to the eyes (RTECS). No other study details were available.

Observation in humans

Mononitrophenols are irritating to the eyes, skin and respiratory tract (see **Acute toxicity: Observations in humans** section).

Sensitisation

Skin Sensitisation

No data are available for the chemical. Quantitative Structure-Activity Relationship (QSAR) data suggest that the likelihood of the chemical being a skin sensitiser is low.

QSAR modelling using OECD QSAR Toolbox (version 4.2) showed that none of the 3 isomers had protein binding alerts for skin sensitisation. Application of skin metabolism and auto-oxidation simulators in the Toolbox showed that the meta and para isomers produced no metabolites of concern, while the ortho isomer produced 1 metabolite with a protein binding alert for skin sensitisation.

Repeated Dose Toxicity

Oral

Limited data are available on the chemical.

Chronic exposure to any of the mononitrophenols in mammals produced changes in neurohumoural regulation; inflammation of the gastro-intestinal track, liver spleen; and nerve damage (HSDB; NTP). Limiting doses for disruption of conditioned reflex activity were established as 0.003 mg/kg bw for 3-nitrophenol (HSDB, NTP).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Observation in humans

Longer term exposure to nitrophenols may lead to cataract formation and growth retardation (HSDBa).

Genotoxicity

While genotoxic potential could not be concluded from the limited data available on the chemical, read across from the structural analogue and metabolite, 3-aminophenol (CAS No. 591-27-5) suggests that the chemical is not likely to be genotoxic.

The following in vitro data are available (CICAD, 2000; NTP):

- The chemical was tested in several bacterial reverse mutation assays in *Salmonella typhimurium*, with inconsistent results seen in strains TA98 and TA100. In the first study, the chemical was not mutagenic in *S. Typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation at 0.01–5 mg/plate. A second study reported that the chemical was weakly positive in *S. Typhimurium* TA98 and TA100, while in a third study the chemical was mutagenic in these 2 strains when tested at similar concentrations.

The following in vivo data are available (CICAD, 2000; NTP):

- The chemical tested negative for reciprocal translocations in sex-linked recessive lethal assay in *Drosophila melanogaster* (NTP).

The following data was available for 1 of the metabolites of the chemical, 3-aminophenol (see **Toxicokinetics** section). Based on weight of evidence of in vitro and in vivo data available, 3-aminophenol was not considered to be genotoxic (NICNASa). Nitroaromatic compounds have to be metabolised to form DNA-reactive species in order to exert their mutagenic potential (National

Institute of Occupational Safety & Health (NIOSH), 1980; Benigni & Bossa, 2011). Reduction of the nitro group in these compounds to hydroxylamine is 1 of the mechanisms by which such DNA-reactive species are formed (Benigni & Bossa, 2011). Mutagenicity of 3-aminophenol is, therefore, considered directly relevant to the chemical.

Carcinogenicity

No data are available for the chemical. Based on the lack of genotoxicity and available data on the metabolite, 3-aminophenol (CAS No. 591-27-5), the chemical is not expected to be carcinogenic.

A significant metabolite of the chemical, 3-aminophenol (see **Genotoxicity** section) is not expected to be carcinogenic based on a non-guideline 2-year dermal study in rats and lack of genotoxicity (NICNASa).

Reproductive and Developmental Toxicity

No data are available for the chemical.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects—serious eye damage and skin irritation; and
- systemic acute effects—acute toxicity on oral and dermal exposures.

Although limited data did not allow for definite conclusions, the following effects cannot be excluded:

- systemic acute effects on inhalation exposure; and
- systemic effects on long-term or repeated exposure.

Public Risk Characterisation

The chemical does not appear to have a cosmetic use in hair dyes in Australia (NICNAS, 2007). International use data indicate that the chemical may not be currently used in cosmetics. While reported to have a cosmetic function in hair dyeing in the EU (CosIng), the chemical is not included in the EU regulation of cosmetic products (Regulation (EC) No. 1223/2009). Similarly, while reported to have a cosmetic function as hair colourant in the US (INCI), the chemical is not listed on any of the US databases for cosmetic products (see **Import, manufacture and use** section). Public exposure to the chemical through cosmetics is not expected.

The commercial use of the chemical in tobacco products, and leather or leather products can potentially be another source of public exposure. However, due to the high cost of manufacture/synthesis of the meta isomer of nitrophenol and the availability of cheaper and more viable alternatives, the use of the chemical in commercial products would be minimal.

In Australia, the chemical is regulated through its inclusion in Schedule 6 of the SUSMP under the group entry for 'NITROPHENOLS'. This measure is considered adequate to minimise any public risk resulting from any potential exposure from commercial products.

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 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 acute, local and long-term (systemic) health effects, the chemical 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

Assessment of this chemical is considered to be sufficient, provided that the recommended amendments to the classification are 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, 2019).

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 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	Harmful if swallowed - Cat. 4 (H302) Toxic in contact with skin - Cat. 3 (H311)
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)

[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 dermal/ocular/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;
- 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.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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