Australian Government

Department of Health and Ageing

National Industrial Chemicals Notification and Assessment Scheme

# INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP)


## HUMAN HEALTH TIER II ASSESSMENT FOR

## Benzene, 1,2-dichloro-4-nitro-

## CAS Registry Number: 99-54-7

# PREFACE

As part of the reform regarding assessment of Existing Chemicals, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is implementing a new framework to address the human health and environmental impacts of industrial chemicals, not yet assessed, on the Australian Inventory of Chemical Substances (AICS).

The framework provides a more rapid, flexible and transparent approach for the assessment of existing chemicals.

The Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework was developed, with significant input from stakeholders, and will be applied in stages.

Stage One of this program, which will take four years, started 1 July 2012 and is examining 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This includes chemicals for which NICNAS already holds exposure information, chemicals identified as a concern or for which regulatory action has been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

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.

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

**For more detail on the new program please visit: www.nicnas.gov.au**

# ACRONYMS & ABBREVIATIONS

| | |
|---|---|
| ACToR | Aggregated Computational Toxicology Resource (US) |
| AICS | Australian Inventory of Chemical Substances |
| ASTDR | Agency for Toxic Substances and Disease Registry (US) |
| bw | bodyweight |
| CAS | Chemical Abstracts Service |
| CFR | Code of Federal Regulations (US) |
| CHO | Chinese hamster ovary |
| CosIng | Cosmetic Ingredients and Substances database (EU) |
| d | day |
| DNA | Deoxyribonucleic acid |
| EC | European Commission |
| EC3 | Estimated concentration three |
| ECHA | European Chemicals Agency |
| ESIS | European Chemical Substances Information System |
| EU | European Union |
| EU RAR | European Union Risk Assessment Report |
| FDA | Food and Drug Administration (US) |
| FSANZ | Food Standards Australia and New Zealand |
| g | gram |
| g/mol | grams per mole |
| GHS | Globally Harmonized System of Classification and Labelling of Chemicals* |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GPMT | Guinea Pig Maximisation Test |
| h | hour |
| HGPRT | hypoxanthine guanine phosphoribosyltransferase |
| HPV | high production volume |
| HSDB | Hazardous Substances Data Bank |
| HSIS | Hazardous Substances Information System |
| HVICL | High Volume Industrial Chemicals List |
| IARC | International Agency for Research on Cancer |
| INCHEM | International Programme on Chemical Safety (also known as IPCS) |
| INCI | International Nomenclature of Cosmetic Ingredients |
| ip | intraperitoneal |
| IRIS | Integrated Risk Information System (US) |
| IUCLID | International Uniform Chemical Information Database |
| iv | intravenous |
| kg | kilogram |
| L | litre |
| LC50 | median lethal concentration |
| LD50 | median lethal dose |
| LCLo | lowest published lethal concentration |
| LLNA | local lymph node assay |
| LOAEL | lowest observed adverse effect level |
| LOEL | lowest observed effect level |
| $m^3$ | cubic metre |
| mg | milligram |
| $mg/cm^3$ | milligrams per cubic centimetre |
| mg/kg bw/d | milligrams per kilogram bodyweight per day |
| min | minute |
| mL | millilitre |
| µg | microgram |
| µL | microlitre |
| (m)SDS | (material) Safety Data Sheet |

| | |
|---|---|
| NIOSH | National Institute for Occupational Safety and Health (US) |
| NOAEC | no observed adverse effect concentration |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |
| NOEL | no observed effect level |
| NOHSC | National Occupational Health and Safety Commission |
| NTP | National Toxicology Program (US) |
| OECD | Organisation for Economic Cooperation and Development |
| OEL | occupational exposure limit |
| PCBU | person conducting a business or undertaking |
| PEL | permissible exposure limit |
| PND | postnatal day |
| ppb | parts per billion |
| PPE | personal protective equipment |
| ppm | parts per million |
| REACH | Registration Evaluation Authorisation of Chemicals (ECHA) |
| SD | Sprague Dawley |
| SIAP | SIDS Initial Assessment Profile (OECD) |
| SIAR | SIDS Initial Assessment Report (OECD) |
| SIDS | Screening Information Data Set (OECD) |
| SMILES | simplified molecular-input line-entry system |
| SPIN | Substances in Preparations In the Nordic countries |
| STEL | short-term exposure limits |
| STV | short-term value |
| SUSMP | Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard**) |
| TCLo | lowest published toxic concentration |
| TEEL | temporary emergency exposure limits |
| TSCA | Toxic Substances Control Act (US EPA) |
| TG | test guideline |
| TGA | Therapeutic Goods Administration |
| TLV | threshold limit values |
| TWA | time weighted average |
| UN | United Nations |
| US | United States of America |
| US EPA | United States Environmental Protection Agency |
| WHS | Work, Health and Safety |
| wt | weight |
| w/w | weight per weight |

**Glossary**

NICNAS uses the IPCS Risk Assessment Terminology (IPCS, 2004) glossary, which includes:
Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment; and
Part 2: IPCS Glossary of Key Exposure Assessment Terminology.
The IPCS Risk Assessment Terminology can be accessed at:
http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

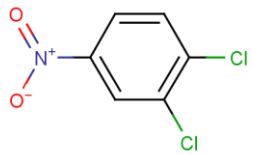
*Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Can be accessed at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

**The Poisons Standard (the SUSMP) can be accessed at: http://www.tga.gov.au/industry/scheduling-poisons-standard.htm

# Benzene, 1,2-dichloro-4-nitro-

**CAS No:** 99-54-7

## Chemical Identity

| | |
|---|---|
| **Synonyms** | 1,2-dichloro-4-nitrobenzene<br>3,4-dichloronitrobenzene<br>1-nitro-3,4-dichlorobenzene<br>Benzene, 1,2-dichloro-4-nitro- |
| **Structural Formula** |  |
| **Molecular Formula** | C6H3Cl2NO2 |
| **Molecular Weight (g/mol)** | 192.0 |
| **Appearance and Odour (where available)** | Solid |
| **SMILES** | c1(Cl)c(Cl)cc(N(=O)=O)cc1 |

## Import, Manufacture and Use

### Australian

No specific Australian use, import or manufacture information has been identified.

### International

The following uses have been identified from REACH Dossiers, Chemica Galleria, and Hazardous Substances Data Bank (HSDB):

- Chemical intermediate for dyes; and
- Chemical intermediate for herbicides (eg Propanil) and insecticides.

## Restrictions

### Australian

No known restrictions have been identified.

### International

No known restrictions have been identified.

## Existing Worker Health And Safety Controls

### Hazard classification

The chemical is not classified on the Hazardous Substances Information System (HSIS) (may be accessed at http://hsis.safeworkaustralia.gov.au/HazardousSubstance). This assessment reviews the data to determine whether classification is required.

### Exposure standards

*Australian*

There are no specific exposure standards for this chemical.

*International*

There are no specific exposure standard for this chemical.

## Health Hazard Information

### Toxicokinetics

It is reported in OECD (2003) that the chemical is absorbed from the gastro-intestinal tract. Although there are some species differences in experimental animals, from the available data it can be concluded that the chemical is excreted mainly via urine in the form of the mercapturic acid derivative N-acetyl-S-(2-chloro-4-nitrophenyl)-L-cysteine.

### Acute Toxicity

***Oral***

The chemical was reported to cause acute toxicity via the oral route (mean lethal dose (LD50) in rats = 625 - 950 mg/kg bw) (OECD 2003). Predominant signs of intoxication included lethargy, increasing weakness, collapse and coma.

***Dermal***

The chemical was reported to cause low acute toxicity via the dermal route (LD50 in rats is > 2000 mg/kg bw) (OECD 2003).

***Inhalation***

No data are available.

### Corrosion / Irritation

***Skin irritation***

The chemical gave no skin irritation effects when tested for 4 hours under semi-occlusive conditions according to OECD TG 404 (OECD 2003). It was noted that slight irritation occurred, which disappeared within 72 hours, under occlusive conditions according to the method of Federal Register 38 No. 187.

***Eye irritation***

The chemical was reported as slightly irritating to the eyes when tested according to OECD TG 405 (OECD 2003). The average scores for cornea / iris / conjunctivae (redness) / conjunctivae (chemosis) were given as 0 / 0.1 / 1.3 / 0.2. The effects were reversible within 72 hrs.

### Sensitisation

***Skin sensitisation***

The chemical was not found to induce dermal sensitisation when tested according to OECD TG 406 (OECD 2003).

***Observation in humans***

In a limited study of 10 female subjects, the single dermal application of a 10 % solution of the chemical in acetone followed by a challenge with a 10 or 0.01 - 1 % solution in acetone on day 28 and 49 was not found to induce dermal sensitisation in humans (OECD 2003).

### Repeat Dose Toxicity

***Oral***

A no observed adverse effect level (NOAEL) of 4 mg/kg bw/d was derived based on changes in red blood cell parameters and haemolytic anemia with microscopic changes in the spleen (OECD 2003; ECHA 2012).

In a repeated dose toxicity study with Wistar rats following the guidelines set out in OECD TG 407, the chemical was administered via gavage to 5 animals/sex/dose at 0, 4, 20 or 100 mg/kg bw/day for 28 days (OECD 2003).

No deaths were observed in either sex during that time. Increased salivation, a slight non-significant increased water intake (in both males and females) and dark yellow discolouration of urine (in males) were observed at dose levels of ≥ 20 mg/kg bw. At dose levels of 100 mg/kg bw/day irregular respiration was seen in both sexes and stilted gait and dark yellow discolouration of urine was observed in females.

Haematological examination revealed significantly reduced haematocrit (mid- and the high-dosed male rats) and significantly increased mean corpuscular volume **(**MCV-values) and number of reticulocytes, both in high-dosed male rats. Female rats showed significantly increased MCV-values at the mid- and the high-dosage only. At necropsy, increased relative liver weights (males: > 12 % from mid-dose onwards, females: > 22 % at high dose group) and spleen weights (males/females: 41 – 70 % at highest dose group), splenic congestion and increased extramedullary haematopoiesis and haemosiderosis were noted. No histopathology changes were reported for the liver. Marked haemosiderosis was seen in mid and high dose groups.

***Dermal***

Studies dealing specifically with dermal repeat dose toxicity were not identified.

***Inhalation***

The no observed adverse effect concentration (NOAEC) following subchronic inhalation exposure study of limited validity (limited documentation) was 0.4 mg/m³ (4 hours per day) (OECD 2003). Given the limited documentation it was difficult to interpret the data in this study.

The chemical was administered via inhalation 0, 0.4, 3.6 or 10 mg/m³ on 4 hrs/day over four months. No deaths were reported. Clinical effects including an increase in methaemoglobinaemia, Heinz bodies and pronounced reticulocytosis and decreases in erythrocyte count and haemoglobin levels at 3.6 mg/m³. At 10 mg/m³ significant increase in serum transaminases, liver catalase and liver diaminooxidase were reported in addition to increased levels of bilirubin in blood and cholesterol in adrenals. There was no histological examination reported in this study.

***Observation in humans***

It is reported in OECD (2003) that changes in haematological parameters (e.g. methaemoglobinaemia, Heinz bodies) are the main target in the only available report on exposure of the chemical to workers. As these findings relate to mixed exposures they cannot be clearly attributed to the chemical, but would be plausible, because they were also observed in animal experiments.

**Genotoxicity**

The chemical is not considered genotoxic.

The chemical exhibits mutagenic activity in Salmonella typhimurium but not in the HPRT test in Chinese Hamster Ovary (CHO) cells (OECD 2003). The chemical induced chromosomal aberrations in V79 cells with metabolic activation only at the highest concentration, which was cytotoxic. In insects (Drosophila melanogaster) the chemical revealed no mutagenic activity in the sex-linked resesive lethal test (SLRL-test) after application over 3 days with slight increased toxicity, but revealed mutagenic activity following a single intraperitoneal injection of a clearly toxic dose (OECD 2003). The chemical also showed no clastogenic activity *in vivo* in a chromosomal aberrations test with rats.

**Carcinogenicity**
No data are available.

**Reproductive and developmental toxicity**
Any reproductive and developmental effects were only observed secondary to maternal toxicity, so the chemical is not a specific reproductive or developmental toxin (OECD 2003).

In a rat teratology study using Sprague-Dawley rats (n = 25 females per group), the chemical was administered via gavage at 0, 10, 30 or 100 mg/kg bw/d from gestation day (gd) 6 – 15. No deaths were observed. A significant dose-response trend for variations (dilated ureters) was seen in the foetuses of ≥ 30 mg/kg bw/day-groups. However, this occurred in the presence of significantly reduced body weight gain of dams at dose levels of 30 mg/kg bw/day on gd 6 - 10 and with an even stronger effect at 100 mg/kg bw/day. Based on the results reported a NOAEL of 10 mg/kg bw/day was determined for maternal and developmental toxicity.

## Risk Characterisation

**Critical Health Effects**
The critical health effects for risk characterisation are repeat dose toxicity and acute toxicity through the oral route.

**Public Risk Characterisation**
Given the use as an intermediate in the manufacture of dyes and other chemicals it is unlikely that public will be exposed to this chemical. Hence, the public risk from this chemical is low.

**Occupational Risk Characterisation**
There is concern for worker health and safety given the acute oral toxicity of the chemical and blood effects observed with repeated exposure at low concentrations in animal studies. Airbourne concentration of the chemical should be kept as low as resonably practicable to minimise risk.

The chemical is used as an intermediate in the manufacture of dyes and other chemicals. Available information from international sources indicate the chemical is well controlled in occupational settings given the chemical is processed in closed systems.

The chemical is not currently classified on HSIS. Hence, the chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls.

## NICNAS Recommendation

The chemical is sufficiently assessed and risk managed provided the current recommendation for classification and labelling is followed.

**Regulatory Control**

***Public Health***
Considering the available information to indicate low public exposure from this chemical, no regulatory controls are recommended.

***Work Health and Safety***
The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This does not consider classification of physical hazards and environmental hazards.

| | *Approved Criteria (HSIS)[a]* | *GHS Classification* |
|---|---|---|
| Acute Toxicity | Harmful if swallowed (Xn; R22) | Harmful if swallowed - Cat. 4 (H302) |

| | | |
|---|---|---|
| Repeat Dose Toxicity | Danger of serious damage to health by prolonged exposure (Xn; R48) | May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373) |

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

* Existing Hazard Classification. No change recommended to this classification.

**Advice for industry**

Work Health and Safety (WHS) legislation in each Australian state and territory imposes obligations on manufacturers and importers of hazardous chemicals to ensure that the chemicals are correctly classified, correctly labelled and (material) safety data sheets ((m)SDS) are prepared for those chemicals. These include:

- the (m)SDS for the chemical, or products and mixtures containing the chemical, must contain accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of a chemical, as well as instructions on the safe storage, handling, use and disposal of the chemical (a review of physical hazards of the chemical has not been undertaken as part of this assessment); and
- a copy of the (m)SDS must be easily accessible to employees.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals to meet duties under the WHS Regulations are provided in the *Preparation of Safety Data Sheets for Hazardous Chemicals—Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively.

To comply with the WHS legislation, a person conducting a business or undertaking (PCBU) at a workplace must manage risks arising from storage, handling and use of a hazardous chemical. Other duties may apply to a PCBU involved in the storage, handling and use of hazardous chemicals at a workplace. Refer to the WHS legislation in the relevant jurisdiction for further information.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice*.

It is recommended that a PCBU should ensure that:

- equipment be designed, constructed, and operated so that, the person handling the chemical does not come into contact with the chemical and is not exposed to a concentration of the chemical that is greater than the workplace exposure standard for the chemical;
- equipment used to handle the chemical retains the chemical, without leakage, at all temperatures and pressures for which the equipment is intended to be used and dispenses or applies the substance, without leakage, at a rate and in a manner for which the equipment is designed.

## References

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