Australian Government
Department of Health and Ageing
NICNAS

# INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP)


## HUMAN HEALTH TIER II ASSESSMENT FOR

## 5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-dioxo-

## CAS Registry Number: 552-30-7

# 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 three 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

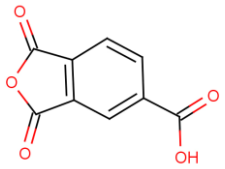
*****Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Can be accessed at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

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

# 5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-dioxo-

**CAS No:** 552-30-7

## Chemical Identity

| | |
|---|---|
| **Synonyms** | Trimellitic anhydride<br>1,2,4-Benzenetricarboxylic anhydride<br>Benzene-1,2,4-tricarboxylic acid 1,2-anhydride |
| **Structural Formula** |  |
| **Molecular Formula** | C9H4O5 |
| **Molecular Weight (g/mol)** | 192.12 |
| **Appearance and Odour (where available)** | - Crystalline colourless solid (HSDB).<br>- Trimellitic anhydride is described as an organic, white to yellow solid, in the form of flakes or tablets, with a pungent odour (REACH Dossier). |
| **SMILES** | C1(=O)c2c(C(=O)O1)cc(C(=O)O)cc2 |

## Import, Manufacture and Use

### Australian

This chemical was reported under previous mandatory and/or voluntary calls for information to be used as an adhesive for construction materials.

### International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, International Program on Chemical Safety Health and Safety Guide (HSG) and the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR).

The chemical was reported to have possible domestic use as a curing agent for epoxy and other resins.

The chemical was reported to have commercial use including:
- in resins for electrodeposition and powder coatings;
- as a binder for glass fibres, sand, and other aggregates;
- as a textile sizing agent;
- as a rubber curing accelerator;
- as an electrostatic toner binder;
- as a vinyl cross-link agent; and
- as an embossing agent for foam-backed vinyl flooring.

The chemical was reported to have site-limited use including:
- the synthesis of trimellitate esters which are used as plasticisers for PVC; and
- the production of polyester resins for water based and conventional solvent-based coatings and paints.

## Restrictions

### Australian

This chemical is listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and

Poisons (SUSMP)) in Schedule 5 as part of a group (Anhydrides, organic acid, for use as curing agents for epoxy resins). Schedule 5 chemicals are labelled with "Caution". These are substances with low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

**International**

This chemical is used as a monomer in polymers in contact with food in accordance with the European Commission Regulation (EU) No 10/2011 of 14 January 2011, in plastic materials and articles intended to come into contact with food. A specific migration limit has been imposed. The United States Food and Drug Administration has established an Acceptable Daily Intake for this substance.

## Existing Worker Health And Safety Controls

**Hazard classification**

Xi; R37 Xi; R41 Xn; R42/43

**Exposure standards**

*Australian*

The chemical has an exposure standard of 0.039 mg/m³ (0.005 ppm) TWA.

*International*

The following exposure standards are identified (Galleria Chemica):
An exposure limit (TWA) of 0.04 mg/m³ (0.005 ppm) in different countries such as USA (national, California, Hawaii), France, Greece, Norway, Germany and Taiwan.

## Health Hazard Information

**Toxicokinetics**

Based on an inhalation study, the estimated biological half-life of the chemical following exposure to 0.95 mg/m³ for 45 minutes ranged from 3 to 46 days, with indications of longer half-lives in males compared to females (OECD, 2002).

**Acute Toxicity**

***Oral***

The chemical was reported to have low acute toxicity via the oral route (LD50 in rats = 2,730 mg/kg bw). Upon necropsy of the animals that died, a number of stomach lesions (*e.g.*, wall thinning, ulcerations, haemorrhage, necrosis) were observed (OECD, 2002).

***Dermal***

The chemical was reported to have low acute toxicity via the dermal route (LD50 in rabbits is > 2000 mg/kg bw and 5,600 mg/kg in rats). Effects noted were consistent with an irritation effect (OECD, 2002).

***Inhalation***

In rats, three out of ten animals died following a four-hour exposure to 2,330 mg/m³ of the chemical, indicating that the acute LC50 value is likely to exceed this concentration. Gross necropsy revealed a number of effects on the lung (*e.g.*, red foci, mottled, fluid-filled) (OECD, 2002).

**Corrosion / Irritation**

***Skin irritation***

Results of studies suggest that the chemical is slightly irritating to skin.

In rabbits, mild irritation (score = 1.7/8.0) was observed following a 500 mg dermal dose of the chemical applied to a 240 cm² patch of pre-moistened skin for 4 hours. Signs of irritation were generally resolved by the end of the observation period (14 days) (OECD, 2002).

***Eye irritation***

The chemical is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi, R41) in HSIS (Safe Work Australia). The available data support this classification. In an eye irritation study in

rabbits, the chemical produced signs of irritation reaching a maximum Draize score of 110/110 at 24 hours following exposure (OECD, 2002).

***Respiratory irritation***

The chemical is currently classified as hazardous in Australia with the risk phrase 'Irritating to respiratory system' (Xi; R37) (Safe Work Australia). The data available support this classification.

In rats, various inhalation exposure studies reported histopathological effects in lung foci, inflammatory cell infiltration and bronchoalveolar pneumonia (OECD, 2002).

In mice, exposure to 0.010, 0.070, or 0.150 mg/m³ for 30 minutes/day for five days produced altered breathing patterns (decreased time of inspiration and expiration, increased length of apnoeic periods). However, no histopathological changes were evident in the lungs of treated animals in this study. Results are consistent with a sensory irritation effect (OECD, 2002).

**Sensitisation**

***Respiratory sensitisation***

The chemical is currently classified as hazardous with the risk phrase ‘May cause sensitisation by inhalation’ (Xi; R42) in HSIS (Safe Work Australia). The data support this classification.

In six long-term occupational studies, observed effects included elevated antibody levels to the chemical in the lungs, asthma, allergic rhinitis and late onset respiratory systemic syndrome (OECD, 2002).

Repeat dose inhalation studies in animals also showed evidence of respiratory sensitisation (see below).

***Skin sensitisation***

The chemical is currently classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (Xi; R43) in HSIS (Safe Work Australia).

Skin sensitisation studies in guinea pigs and rodents produced variable results depending upon whether the chemical was dissolved in a solvent prior to exposure to test animals. The presence of a solvent increases the dermal sensitisation potential of the chemical. While under normal conditions of manufacture and use, the chemical is likely to be a powder and would not be used in a solvent, it should be considered as a potential dermal sensitiser (OECD, 2002).

**Repeat Dose Toxicity**

***Oral***

The toxicity of the substance following repeated oral exposures is low, based on NOAELs of approximately 500 mg/kg/day identified for both rats and dogs (OECD, 2002; REACH, 2013).

***Inhalation***

Based on the available information, no hazard classification for repeat dose inhalation toxicity is recommended. However, the classification for respiratory sensitisation is supported in the animal studies.

In repeated dose inhalation studies, the principal effects of the substance are on the immune system and the lung. In a 13 week inhalation repeat dose study, a dose dependent increase in antibody levels and lung lesions (haemorrhagic foci, inflammatory cell infiltration, bronchoalveoloar pneumonia) were observed in rats following exposures to relatively low concentrations (0.002 - 0.054 mg/m³) for 6 hours/day, five days/week. A NOAEL was not identified. Mechanistic studies demonstrate that when the immune system of rats is suppressed, exposure to this substance does not produce lung lesions (OECD, 2002).

**Genotoxicity**

Data from in vitro studies using bacteria and Chinese hamster ovary cells were consistently negative, suggesting that the potential for significant genotoxicity is low (OECD, 2002).

### Reproductive and developmental toxicity

Based on the limited information available, the chemical is not likely to be a reproductive or developmental toxin.

Reproductive performance was not affected in female rats and guinea pigs following exposure to concentrations of 0.5 mg/m³ on days 6 to 15 of gestation. Data available from other studies also suggest that the potential for significant reproductive toxicity is low. For example, subchronic oral and inhalation exposure studies in rats and dogs using doses of approximately 500 mg/kg/day did not result in any histopathological effects to reproductive tissues (OECD, 2002).

## Risk Characterisation

### Critical Health Effects

The critical health effect for risk characterisation is respiratory sensitisation. The chemical may also cause other local effects including, eye and respiratory tract irritation and skin sensitisation.

### Public Risk Characterisation

Given the uses identified for this chemical, it is unlikely that the public will be exposed to this chemical with the possible exception of its use as a hardener in epoxy resin. Although the public may come into contact with articles/coated surfaces containing residual amounts of this chemical, it is expected that the chemical will be bound within the article/coated surface and hence will not be bioavailable. Inhalation exposure to the chemical as a component of an epoxy hardener is not expected, therefore the risk to the public is not considered to be unreasonable.

### Occupational Risk Characterisation

During formulation of products, dermal, ocular and inhalation exposure of workers to the chemical may occur particularly where manual or open processes are used. This may include during transfer and blending activities, quality control analysis and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur during the use of formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic local effects of the chemical, the chemical may pose an unreasonable risk to workers if adequate control measures to minimise inhalation exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace has adequate information to determine appropriate controls.

Based on the available data the hazard classification in HSIS is considered appropriate.

## NICNAS Recommendation

Current risk management measures are considered adequate for the protection of public and workers' health and safety provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

### *Occupational 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*** |
|---|---|---|
| Irritation / Corrosivity | Risk of serious eye damage (Xi; R41)*<br>Irritating to respiratory system (Xi; R37)* | May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335) |
| Sensitisation | May cause sensitisation by inhalation (Xn, R42)*<br>May cause sensitisation by skin contact (Xi; R43)* | May cause an allergic skin reaction - Cat. 1 (H317) |

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

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

## Advice for industry

### *Control measures*

Control measures to minimise the risk from 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 storage, handling and use of a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include but are not limited to:

- use of closed systems or isolation of operations;
- use of 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;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of 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 assist with meeting 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 hazardous chemical are prepared; and
- management of risks arising from storage, handling and use of 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 physical hazards of the chemical has not been undertaken as part of this assessment.

## References

IPCS INCHEM 1992. Health Safety Guide on Trimellitic anhydride (552-30-7). Accessed March 2013 at http://www.inchem.org/documents/hsg/hsg/hsg71.htm.

OECD 2002. SIAR on Trimellitic anhydride (TMA) (552-30-7). Accessed March 2013 at http://webnet.oecd.org/hpv/UI/handler.axd?id=be6d8c15-085e-4a6b-8ba0-46585019401d.

REACH Dossier 2013. Benzene-1,2,4-tricarboxylic acid 1,2-anhydride (552-30-7). Accessed March 2013 at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8a0574-c000-6534-e044-00144f67d249/AGGR-1b043174-a15a-409b-bdce-f79197128f06_DISS-9d8a0574-c000-6534-e044-00144f67d249.html#section_3_5.