Tetrahydrophthalic anhydrides and analogues: Human health tier II assessment

27 October 2017

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-	85-43-8
1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-5-methyl-	3425-89-6
1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-4-methyl-	5333-84-6
1,3-Isobenzofurandione, tetrahydromethyl-	11070-44-3
1,3-Isobenzofurandione, tetrahydro-	26266-63-7
1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydromethyl-	26590-20-5

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 are tetrahydrophthalic anhydrides (THPA). This group definition includes *cis*- and *trans*-stereoisomeric forms, or any combination (reaction mass, or unknown or variable composition, complex reaction products and biological materials (UVCB) substance).

The uses of the chemicals and their hazardous properties (ocular corrosivity; and potency for skin and respiratory sensitisation) are expected to be driven by the acid anhydride functional group (ECHA, 2012). The presence of a methyl group in methyltetrahydrophthalic anhydride (MTHPA) compounds is not expected to greatly affect the toxicity of the chemicals and thus, these chemicals are included as structurally-similar analogues under this group definition (EU CLPa; EU CLPb; REACHa; REACHb; REACHc; REACHd).

Animal and human data for other structurally-relevant cyclic acid anhydrides including hexahydromethylphthalic anhydride (MHHPA) (CAS Nos. 19438-60-9 and 57110-29-9); hexahydrophthalic anhydride (HHPA) (CAS No. 85-42-7); and to a lesser extent, trimellitic anhydride (TMA) (CAS No. 552-30-7) are considered relevant as analogue data (NICNASa; NICNASb; NICNASc) and will be used for read-across where hazard data are lacking.

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; and Substances and Preparations in the Nordic countries (SPIN) database.

The main use for the chemicals are as hardeners for epoxy resins (OECD, 2002). In general, organic acid anhydrides are commercially-available at high purity as liquids or crystals (dependent on the specific anhydride). Technical grade anhydride products may contain other related cyclic anhydrides as impurities or they can be mixtures of different isomers, e.g. technical grade MHHPA may contain 4.2 % MTHPA (ECHA, 2012; NICNASb).

Cyclic acid anhydrides are used in the manufacture of polyester and alkyd resins, and as plasticisers for thermoplastic polymers, hardeners for epoxy resins and chain cross-linkers for thermoplastic polymers (ECHA, 2012; NICNASb).

The chemicals have reported potential domestic uses, including in:

- fillers;
- adhesives (binding agents); and
- paints, lacquers and varnishes.

These specific uses may, in some cases, be restricted to commercial applications. The chemicals were not listed on the United States (US) Department of Health and Human Services, Household Products Database, indicating that the chemicals are not likely to be widely available in domestic products.

The chemicals have reported commercial uses, including:

- in the formulation of hardeners for epoxy resins;
- as process regulators;
- in viscosity adjusters; and
- in heat transferring agents.

The chemicals have reported site-limited uses as chemical intermediates, e.g. in the manufacture of other chemicals including polyesters, plasticisers, adhesives, light coloured alkyds and resin hardeners.

Restrictions

Australian

There are no specific entries in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2017) for any of the chemicals.

There is a general entry for 'ANHYDRIDES, ORGANIC ACID for use as curing agents for epoxy resins **except** when separately specified in these Schedules' in the SUSMP in Schedule 5 (SUSMP, 2017). This entry covers all the chemicals in the group when used as curing agents for epoxy resins.

Schedule 5 chemicals are described as 'Substances with a 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.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2017).

International

Listings for THPA (CAS No. 85-43-8) and MTHPA (CAS No. 26590-20-5) on the 'United Nations Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or Not Approved by Governments (Sweden)' (Galleria Chemica).

There is also a listing for THPA on the 'United Arab Emirates Restricted Chemicals List' (Galleria Chemica).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group are each individually classified as hazardous, and each has the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Eye damage – category 1; H318 (Causes serious eye damage);

Skin sensitisation – category 1; H317 (May cause an allergic skin reaction); and

Respiratory sensitisation – category 1; H334 (May cause allergy or asthma symptoms or breathing difficulties if inhaled).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 3 mg/m^3 time weighted average (TWA) in Denmark and Russia was reported for THPA (CAS No. 85-43-8).

An exposure limit of 0.05–1 mg/m^3 TWA in Japan and Russia was reported for MTHPA (CAS No. 11070-44-3).

The following temporary emergency exposure limit (TEEL) values are listed by the United States of America (USA) Department of Energy (DOE) (Galleria Chemica).

THPA:

- 16 mg/m^3 for TEEL-1;
- 180 mg/m^3 for TEEL-2; and

- 1100 mg/m^3 for TEEL-3.

MTHPA:

- 7.7 mg/m^3 for TEEL-1;
- 85 mg/m^3 for TEEL-2; and
- 510 mg/m^3 for TEEL-3.

Health Hazard Information

The information presented in this section is based on the reported hazards of tetrahydrophthalic anhydrides and analogues, which includes the isomers in this assessment. All of these chemicals are expected to have similar toxicity based on the anhydride group.

Toxicokinetics

No animal data are available. Following inhalation exposure in humans, MTHPA is reported to be metabolised into the di-carboxylic acid and excreted in urine. The half-life for excretion is reported to be 3–6 hours (OECD, 2002).

It is reported that HHPA and other acid anhydrides are reported to hydrolyse rapidly and are expected to be present as the diacid hydrolysis product in the systemic circulation. HPPA is readily absorbed following respiratory exposure and can be found in the plasma after absorption, with excretion via the urine (NICNASb).

Acute Toxicity

Oral

Based on available data for THPA and MHTPA (unspecified CAS Nos.), the chemicals are considered to have low acute oral toxicity.

The oral median lethal dose (LD50) was reported to be >2000 mg/kg bodyweight (bw) in male and female Crj:CD Sprague-Dawley (SD) rats exposed to THPA and MTHPA based on 2 studies (equivalent to OECD TG 401 (acute oral toxicity)). Reported treatment-related effects to MTHPA included inflammation of the forestomach, including thickening of the mucosa, squamous hyperplasia and granulomatous inflammation. No mortality was reported (REACHa; REACHd; OECD, 2002).

In a non-guideline study, the oral LD50 was reported to be 1900 mg/kg bw in male and female Crj:CD (SD) rats administered MTHPA (REACHd; OECD, 2002).

Dermal

Based on available data for THPA and MTHPA (unspecified CAS Nos.), the chemicals are considered to have low acute dermal toxicity.

The dermal LD50 was reported to be >2000 mg/kg bw in male and female SD rats exposed to THPA and MTHPA, based on 2 studies (equivalent to OECD TG 402 (acute dermal toxicity)). No treatment-related effects were reported (REACHa; REACHd; OECD, 2002).

In 2 non-guideline studies in rabbits, the dermal LD50 was reported to be >242 or >1210 mg/kg bw (following 0.4 or 2 mL dermal application of MTHPA); and >1706 mg/kg bw (equivalent to 1.41 mL/kg (unspecified dermal application of MTHPA)). No further study details are available (REACHd; OECD, 2002).

Inhalation

No data are available for the chemicals. Based on the available data for the analogues HHPA (CAS No. 85-42-7) and TMA (CAS No. 552-30-7), the chemicals are considered to have low acute inhalation toxicity.

It is reported that HHPA and TMA have low acute toxicity following inhalation (median lethal concentration (LC50) values >1100 and >2330 mg/m^3 in rats, respectively) following 4 hours of exposure (NICNASb; NICNASc).

Corrosion / Irritation

Skin Irritation

Based on available data for THPA and MHTPA (unspecified CAS Nos.) and for the analogues HHPA and TMA (refer to **Irritation: Observations in Humans** section), the chemicals are considered to be slightly irritating to the skin.

In a study conducted similarly to OECD TG 404 (acute dermal irritation/corrosion), 0.5 mL of THPA (as aqueous solution (>99 % purity)) was applied to the shaved skin of white Russian rabbits (3 animals/group) for 4 hours under semi-occlusive patches over a 6 day observation period. Observations were made at 24–72 hours post-treatment. Slight erythema was reported (mean erythema Draize scores of 0.43 during the period 24-72 hours following treatment). Treatment-related effects were reversible within 72 hours (REACHa). Dissolution in aqueous solution is expected to hydrolyse the anhydride group, and thus this study may not be truly representative of the irritating potential of the chemical.

In a non-guideline study, MTHPA (0.5 mL of unspecified purity; no vehicle) was applied to the abraded skin and the intact skin of 6 rabbits (unspecified strain) for 24 hours, under occlusive patches. Animals were observed at 24 and 72 hours after the patch removal. The mean erythema Draize scores (24–72 hours) for intact and abraded skin were reported to be 2.00 and 1.58, respectively. The mean oedema Draize scores (24–72 hours) for intact and abraded skin were reported to be 1.92 and 1.50, respectively. A primary dermal irritation index score of 3.5 was reported. No further study details were available; however, the authors concluded that MTHPA was not classifiable as a skin irritant under these study parameters (REACHd; OECD, 2002).

It is reported that HPPA is considered to be slightly irritating to the skin of rabbits at a concentration of 50 % (in separate vehicles; mineral oil and polyethylene glycol) using a 24 hour exposure period. Irritation effects were reported to be reversible after 72 hours. No Draize scores were provided (NICNASb).

Mild skin irritation was reported in a non-guideline study using a 4-hour exposure, when 500 mg of TMA was applied to rabbit skin. Irritation effects were reversible within the 14-day observation period (NICNASc).

Eye Irritation

Based on available data for THPA and MTHPA (unspecified CAS Nos.), the chemicals are considered to be eye irritants. There are insufficient data to warrant downgrading the existing classification.

In a study conducted according to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of THPA (no vehicle; >99 % purity) was instilled into the conjunctival sac of 1 white Russian rabbit, single exposure. Draize scores of 2 (one hour post-exposure) were reported for corneal opacity, iritis, redness of the conjunctivae and chemosis. The study was terminated after 1 hour due to the severity of the ocular reaction (REACHa).

In a study conducted similar to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of MTHPA (undiluted and diluted 1:10 in olive oil; >99 % purity) was instilled into the conjunctival sac of 2 Belgian hares over a 10-day observation period (duration of treatment/exposure unspecified). The eyes of the animals were not rinsed. Clouding of the cornea was reported 1 minute post-exposure in eyes' of animals treated with undiluted MTHPA. A mean eye irritation score of 3 for overall irritation and corneal opacity was reported at 1 minute. At 24 hours post-exposure, eye irritation scores were 1, 0 and 0 for iritis, redness of the conjunctivae and chemosis, respectively. Ten days post-exposure, a chemosis score of 1 was noted. Corneal irritation effects (including redness of the iris at 24 hours) did not resolve within the observation period but were reported to be reversible within

14 days. Treatment-related effects were also reported in the eyes' of animals treated with diluted MTHPA but were reversible within the observation period (REACHd; OECD, 2002).

Observation in humans

In a case study, 3 workers had nasal and/or skin complaints following exposure to MHHPA and HHPA. Nasal pain and rhinorrhoea were reported in 1 worker as a result of an irritation reaction (Yokota et al, 2001).

Sensitisation

Respiratory Sensitisation

Limited data are available for the chemicals (refer to **Sensitisation: Observation in Humans** section) and for the analogues MHHPA, HHPA and TMA. Based on the weight of evidence, the chemicals are considered to be respiratory sensitisers.

In a respiratory sensitisation study, guinea pigs intradermally exposed to HHPA (unspecified concentration) and then challenged by inhalational exposure exhibited effects consistent with a respiratory allergic response (e.g. bronchial obstruction/spasm, secretion and oedema). Recovery from respiratory effects was reported to occur within 30 minutes (NICNASb).

In another study, HHPA triggered a dose-dependent increase in specific IgG responses in guinea pigs (effects consistent with induced respiratory allergy). Following intratracheal instillation, immediate effects on the airways (lasting up to 6 minutes) were reported (NICNASb).

Mice (unspecified strain) exposed to HHPA for 3 days had a Th2 lymphocyte-mediated immune response, consistent with an allergic respiratory response (NICNASb).

The ECHA (2012) reports that the effects of exposure to MHHPA, with regard to respiratory sensitisation, can be compared to non-threshold carcinogens in that it is difficult to establish a ‘safe’ threshold dose. Following, prolonged exposure, MHHPA may cause serious and permanent impairment of lung functions and MHHPA-induced sensitisation is irreversible.

The chemicals presented protein binding alerts for skin sensitisation (acylation: direct acylation involving a leaving group) and respiratory sensitisation (acylation: ring opening acylation at a carbonyl) based on their molecular structures as profiled by the OECD Quantitative Structure–Activity Relationship (QSAR) Toolbox v3.4.

The QSAR modelling using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue MEtabolism Simulator; version 2.27.19) predicted positive results for skin and respiratory sensitisation (protein acylation by anhydrides and related sulfur analogues) for the chemicals. However, the chemical was out of the applicability domain of the model used for these predictions, indicating greater uncertainty about the reliability of the results.

Skin Sensitisation

Based on available data for THPA and MHTPA (unspecified CAS Nos.) and for the analogues MHHPA, HHPA and TMA (refer to **Sensitisation: Observation in Humans** section), the chemicals are considered to be skin sensitisers.

In a guinea pig maximisation test (GPMT) conducted according to OECD TG 406 (skin sensitisation), female Dunkin-Hartley guinea pigs (20/dose) were intradermally induced with a 0.5 % (v/v) solution of THPA in maize oil. The animals were topically induced via a topical application with THPA (concentration of 100 %) 1 week later. A concentration of 100 % was used in the topical challenge phase (occlusive epicutaneous application) 2 weeks after topical induction. Positive results for sensitisation were reported in 17/20 animals (24 and 48 hours post-exposure) when challenged (REACHa).

It is reported that HHPA (unspecified concentration) was a skin sensitiser based on a GPMT. A positive response for skin sensitisation was observed in 17 out of 20 animals (85 %). In another skin sensitisation study, Hartley guinea pigs exposed intradermally to HHPA and other organic acid anhydrides (single dose; 0.3 M solution) developed both specific IgG and IgE antibodies to HHPA. No further study details (including the concentration of HPPA used for testing) were available (NICNASb).

Potential skin sensitisation to TMA was reported in guinea pigs and rodents. The presence of a solvent increased the dermal sensitisation potential of the chemical (NICNASc).

Observation in humans

Respiratory sensitisation and/or skin sensitisation can be caused through exposure to MTHPA and other organic acid anhydrides (including MHHPA, HHPA and TMA) in humans. There are a number of documented case studies of workers exposed to the chemicals and immunological investigations have been reported below.

It is reported that MTHPA was sensitising at calculated concentrations of 20-150 µg/m^3 with reported eye and nasal signs and symptoms such eye and pharynx pain, sneezing, nasal secretion and blockage, cough and asthma. In workers exposed to MTHPA, the specific IgE levels were high and closely related to the signs and symptoms. The Japanese Society for Occupational Health has recommended 50 µg/m^3 (TWA) as a limit for exposure to this substance during an 8 hour work shift (refer to **Existing Worker Health and Safety Controls: Exposure Standards** section) (REACHd; OECD, 2002).

In a study designed to determine the efficacy of workplace hygiene measures, workers exposed to HHPA and MTHPA were examined for sensitisation reactions. In the initial assessment, 20/110 workers examined prior to workplace initiatives to reduce exposure, were sensitised (either specific IgE for MTHPA and/or HHPA or positive skin prick testing were reported). In a follow-up examination, sensitisation to MTHPA was confirmed in all workers who initially tested positive (specific IgE levels for 'HHPA' were not reported). An additional group that initially tested negative for skin sensitisation, but had worked at the plant prior to the workplace initiatives to reduce exposure, also tested positive for sensitisation to MTHPA. None of the examined workers who began their employment after the workplace initiatives to reduce exposure were introduced, were found to be sensitised to MTHPA in the follow-up study (ECHA, 2012; NICNASb).

In a case study of 3 workers with nasal and/or skin complaints who had been exposed to MHHPA and HHPA, the symptoms in 1 worker (nasal pain and rhinorrhoea) were considered to be a result of an irritation reaction. A second worker with similar levels of exposure reported symptoms of severe rhinitis and cough, but symptoms were reversible post-exposure. Despite negative results for specific IgE and patch tests, this worker was reported to be sensitised to MHHPA. The third worker demonstrated rhinitis and urticaria and tested positive for specific IgE for phthalic anhydride and HHPA (ECHA, 2012; NICNASa). A 20-minute closed patch test with MHHPA was positive (Yokota et al, 2001).

In a study investigating the exposure relationships of MHHPA and HHPA for sensitisation and effects to the airway, a close association between test results for MHHPA and HHPA was reported due to cross-sensitivity (ECHA, 2012; NICNASa).

A worker with a history of childhood asthma and atopy experienced chest tightness, coughing and wheezing 4-5 minutes after exposure to HHPA fumes. Another worker exposed to airborne MHHPA and HHPA was diagnosed with occupational contact urticaria, rhinitis and conjunctivitis (ECHA, 2012; NICNASa).

In an investigation of workers exposed to HHPA, nasal challenge tests indicated that 11 subjects with work-related nasal symptoms were sensitised to HHPA, based on positive skin prick tests and positive radioallergosorbent tests (which screens for IgE mediated allergy). Workers also had decreased nasal inspiratory peak flow and an increase in signs and symptoms following challenge. Out of 20 unsensitised workers (11 without symptoms and 9 with work related nasal symptoms), there were no significant changes to any of the tested parameters (ECHA, 2012; NICNASa).

In a dermal sensitisation study using a 5 % solution of HHPA in mineral oil, 4/53 patients showed low grade sensitivity and 1/53 patients showed a marked reaction to HHPA, demonstrating skin sensitisation (ECHA, 2012; NICNASa).

It is reported that TMA caused respiratory sensitisation based on evidence from repeat dose inhalation studies (refer to **Repeated Dose Toxicity: Inhalation** section) and in 6 long-term occupational studies. Observed effects in occupational studies included: elevated antibody levels in the lungs, asthma, allergic rhinitis and late onset respiratory systemic syndrome (NICNASc).

Repeated Dose Toxicity

Oral

Based on data available on THPA and MTHPA (unspecified CAS Nos.), the chemicals are not considered to cause adverse health effects following repeated oral exposure.

In a repeat dose 28-day oral gavage study (OECD TG 407), THPA was not considered to cause severe systemic toxicity in male and female SD rats (n = 10/sex/dose; except at the highest dose where n = 20/sex) following repeated oral exposure up to 600 mg/kg bw/day. No treatment-related signs of systemic toxicity were reported. A no observed adverse effect level (NOAEL) of 100 mg/kg bw/day was reported based on local effects (stomach lesions at the higher doses of 250 and 600 mg/kg bw/day). An NOAEL of 600 mg/kg bw/day was reported for systemic effects (no systemic effects were observed at the highest dose) (REACHa).

In a combined repeated dose/reproductive/developmental oral toxicity study (OECD TG 422) in male and female Crj:CD (SD) rats (refer to **Reproductive & Developmental Toxicity** section), the NOAEL for systemic toxicity for MTHPA was reported to be 100 mg/kg bw/day for both sexes (based on altered clinical chemistry parameters, changes in organ weights and inflammation of the forestomach mucosa at 300 mg/kg bw/day, the highest dose tested) (REACHd; OECD, 2002).

Dermal

No data are available for the chemicals.

Inhalation

No data are available for the chemicals. Based on the limited data for the analogue TMA, the chemicals are not considered to cause adverse health effects following repeated inhalation exposure.

In a repeated dose 90-day inhalation toxicity study, rats were exposed to TMA at concentrations of 0.002–0.054 mg/m^3 for 6 hours/day, 5 days/week. Dose-dependent increases in antibody levels and lung lesions (haemorrhagic foci, inflammatory cell infiltration, bronchoalveolar pneumonia) were reported. A no observed adverse effect concentration (NOAEC) was not identified. Mechanistic studies demonstrate that when the immune system of rats is suppressed, exposure to TMA does not produce lung lesions (NICNASc).

Genotoxicity

Based on the available in vitro data on THPA and MTHPA (unspecified CAS Nos.), the chemicals are not considered to be genotoxic. Whilst no in vivo data were available, the weight of evidence from the analogues HHPA and TMA indicate the chemicals are not likely to be genotoxic.

In the following study summaries, several in vitro assays using THPA and MTHPA gave mostly negative results (REACHa; REACHd; OECD, 2002):

- negative results in bacterial reverse mutation assays in *Salmonella typhimurium* strains TA 98, TA 100, TA1535 and 1537, with or without metabolic activation at concentrations up to 5000 µg/plate;
- negative results in bacterial reverse mutation assays in *Escherichia coli* strains (WP2uvrA), with or without metabolic activation at concentrations up to 5000 µg/plate;
- negative results in chromosomal aberration assays in human lymphocyte cells, and Chinese hamster lung fibroblasts (V79) cells, with or without metabolic activation, at concentrations up to 1520 µg/mL and 156.25 µg/mL, respectively;
- mixed results in chromosomal aberration assays in Chinese hamster lung (CHL/IU) cells, with or without metabolic activation at concentrations up to 1700 µg/mL; and
- negative results in a mammalian cell gene mutation assay in mouse lymphoma L5178Y (TK+/TK-) cells, with or without metabolic activation at concentrations up to 1520 µg/mL and 3000 µg/mL.

The chemical structures did not give DNA binding alerts for genotoxicity as profiled by the QSAR Toolbox v3.4.

The QSAR modelling using OASIS–TIMES (version 2.27.19) predicted negative results in vitro (Ames and chromosomal aberration) and negative results in vivo (micronucleus test and liver genotoxicity) for genotoxicity. However, the chemicals were out of the applicability domain of the model used for these predictions, indicating greater uncertainty about the reliability of the results.

It was reported that HHPA and TMA were negative for mutagenicity in vitro, both in bacterial and mammalian cells, with or without metabolic activation. No in vivo genotoxicity data was available (NICNASb; NICNASc).

Carcinogenicity

No data are available for the chemicals.

The chemical structures did not contain an alert for genotoxic carcinogenicity as profiled by the OECD QSAR Toolbox v3.4.

Reproductive and Developmental Toxicity

Based on data available for THPA and MTHPA (unspecified CAS Nos.), the chemicals are not expected to cause reproductive or developmental toxicity.

In a reproductive/developmental toxicity study (OECD TG 421) in SD rats (n = 10/sex/dose) administration of THPA by oral gavage did not cause significant treatment-related adverse effects on reproductive and developmental parameters at doses up to 600 mg/kg bw/day. Treatment-related effects on pregnancy, including prolonged gestation period and smaller litter size were reported in the highest dose group. The NOAEL for reproductive toxicity was reported as 250 mg/kg bw/day (REACHa).

In a combined repeated dose and reproductive/developmental oral toxicity study (OECD TG 422), MTHPA was administered to Crj:CD (SD) rats daily by oral gavage at doses of 0, 30, 100 or 300 mg/kg bw/day for 49 days (males) and 2 weeks prior to mating (females), up until day 3 of lactation. No treatment-related adverse effects on reproductive or developmental parameters were reported up to the highest dose tested. The NOAEL for reproductive toxicity was reported as 300 mg/kg bw/day for both sexes (REACHd; OECD, 2002).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (skin and respiratory sensitisation and severe eye irritation).

Public Risk Characterisation

In the absence of Australian use information, the international uses indicated some potential domestic uses (in adhesives (binding) agents, paints, lacquers and varnish products). Available information indicates the chemicals are unlikely to be used in domestic products in these categories.

The chemicals are covered by the Schedule 5 general group entry for 'ANHYDRIDES, ORGANIC ACID' in the SUSMP for use as curing agents for epoxy resins (SUSMP, 2017). The chemicals may also be present in reacted form in consumer items manufactured from plastics (such as food packaging, storage, mobile phones, toys etc.), but the chemically reacted products will not regenerate the chemicals under any conditions.

Given the lack of Australian uses identified for these chemicals and based on the international information, it is unlikely that the public will be exposed, except at very low levels for uses covered by the existing Poisons Standard Schedule 5 entry (SUSMP, 2017). Hence, the public risk from these chemicals is not considered to be unreasonable. If information becomes available to indicate the chemicals are used in domestic products in Australia (which could indicate potential public exposure), further regulatory controls may need to be implemented to protect the general public from the identified health hazards.

Occupational Risk Characterisation

Given the critical health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalational exposure are implemented. The chemicals should be appropriately 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.

There is no current Australian exposure standard that applies to the chemicals. Based on the available information regarding the health risk to exposed workers, respiratory allergy is a major concern arising from the industrial use of the chemicals. There may be no level of exposure that does not present an increased risk of adverse respiratory effects (ECHA, 2012).

The chemicals are appropriately classified to implement control measures to prevent worker inhalation, ocular and dermal exposure. The controls that should be in place due to the respiratory sensitisation classification are expected to be sufficient to protect workers from any potential systemic effects.

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate for the chemicals.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and worker 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.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2017).

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonised 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]
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318)*
Sensitisation	Not Applicable	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334)* May cause an allergic skin reaction - Cat. 1 (H317)*

[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 dermal, ocular and inhalational 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 27 October 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-** tetrahydrophthalic anhydride (THPA) 1,2,3,6-tetrahydrophthalic anhydride 4-cyclohexene-1,2-dicarboxylic anhydride maleic anhydride adduct with butadiene memtetrahydro phthalic anhydride
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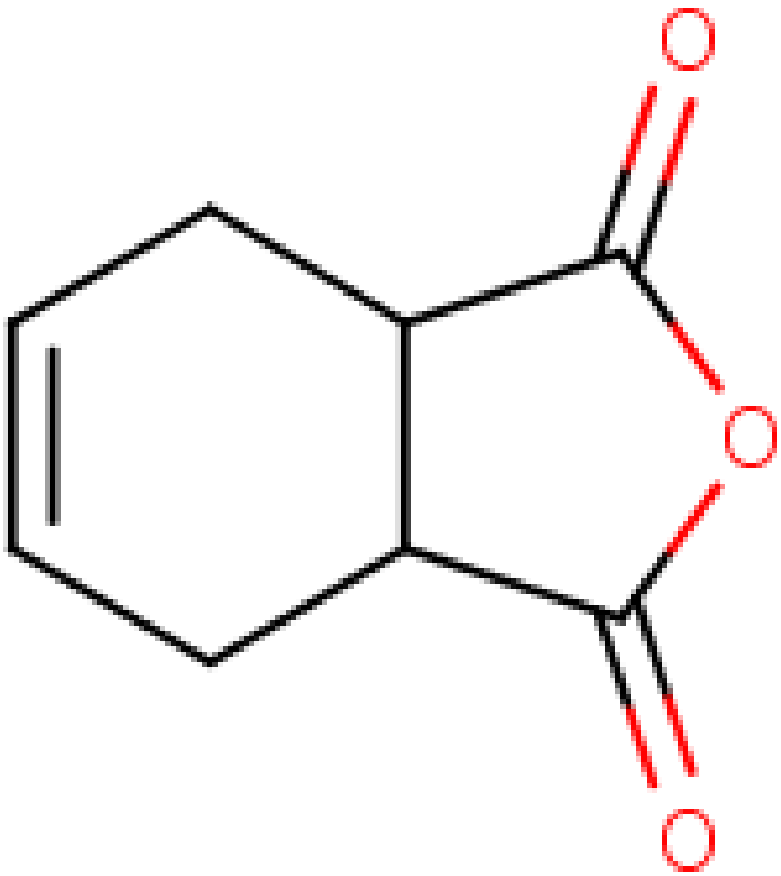
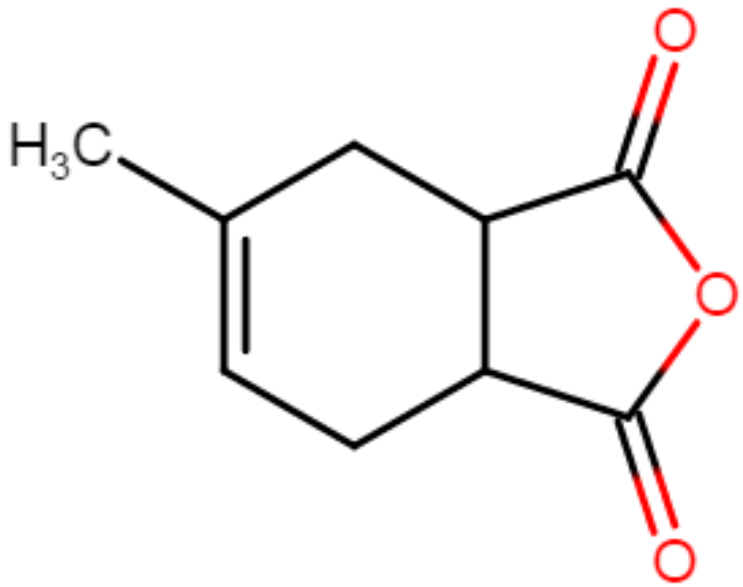
Structural Formula	
Molecular Formula	C8H8O3

Molecular Weight	152.15

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-5-methyl-** 4-methyltetrahydrophthalic anhydride (4-MTHPA) 4-methyl-delta-4-tetrahydrophthalic anhydride isomethyltetrahydrophthalic anhydride 4-cyclohexene-1,2-dicarboxylic anhydride, 4-methyl- 1,2,3,6-tetrahydro-4-methylphthalic anhydride
CAS Number	3425-89-6
Structural Formula	
Molecular Formula	C9H10O3
Molecular Weight	166.18

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-4-methyl-** 3-methyltetrahydrophthalic anhydride (3-MTHPA) 1,2,3,6-tetrahydro-3-methylphthalic anhydride maleic anhydride, 1,3-pentadiene adduct 4-cyclohexene-1,2-dicarboxylic anhydride, 3-methyl- 1,3-isobenzofurandione, 3a,4,7,7a-tetrahydro-4-methyl-
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	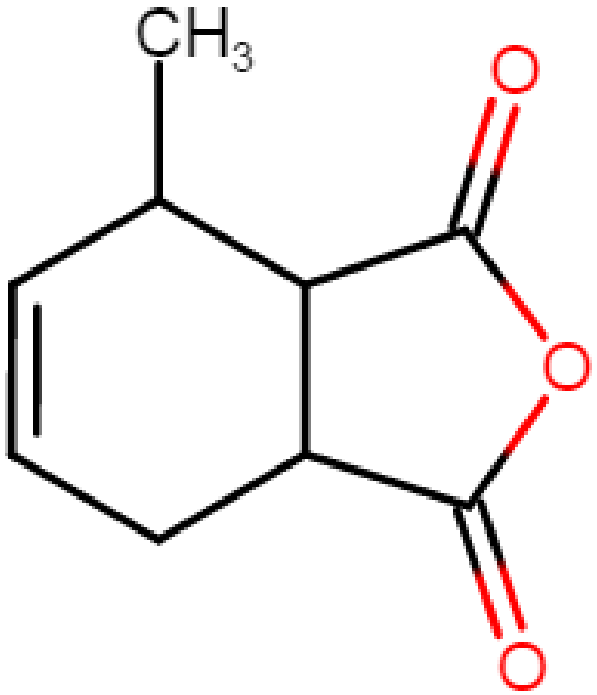
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Molecular Weight	166.175

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, tetrahydromethyl-** methyltetrahydrophthalic anhydride (MTHPA) tetrahydromethylphthalic anhydride
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	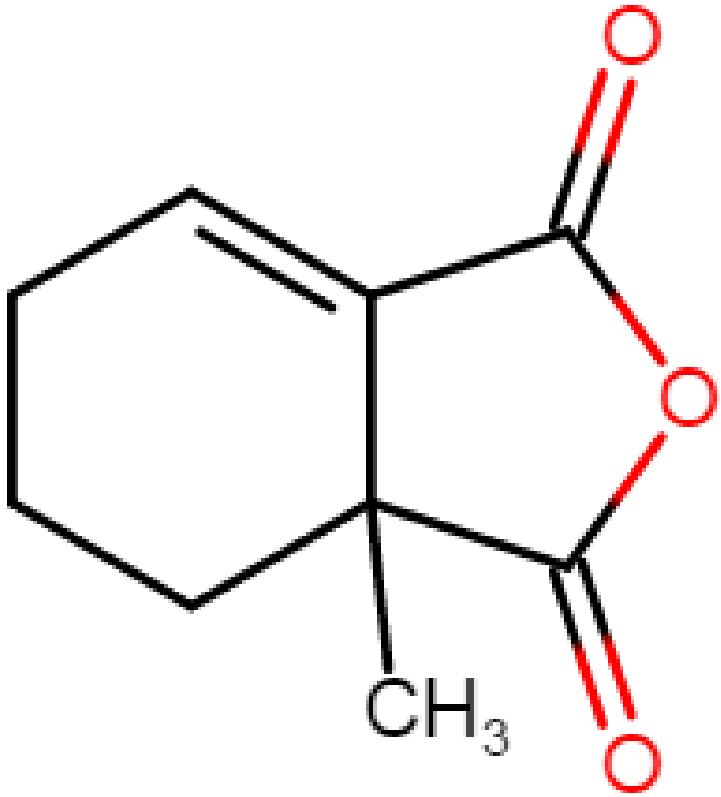
Molecular Formula	C9H10O3
Molecular Weight	166.18

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, tetrahydro-** tetrahydrophthalic anhydride (THPA)
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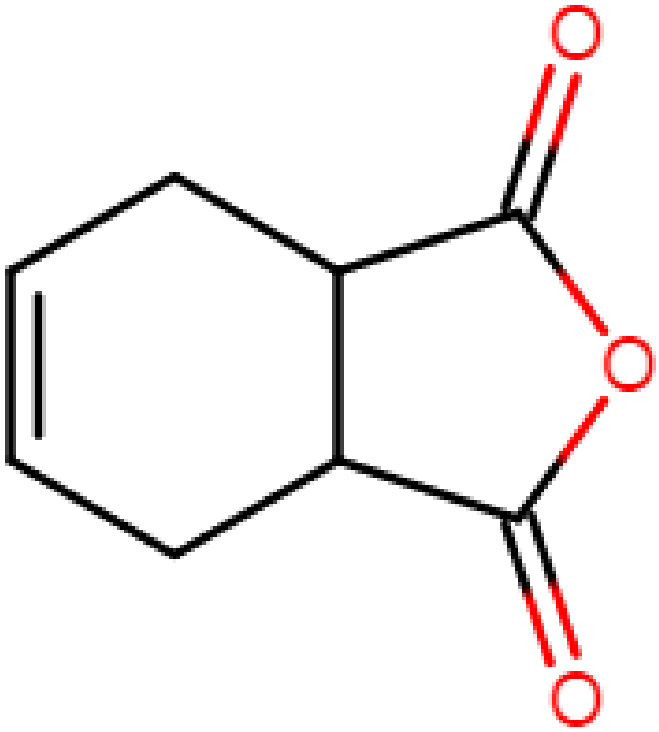
Structural Formula	

	
Molecular Formula	C8H8O3
Molecular Weight	152.15

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydromethyl-** methyltetrahydrophthalic anhydride (MTHPA) 1,2,3,6-tetrahydromethylphthalic anhydride
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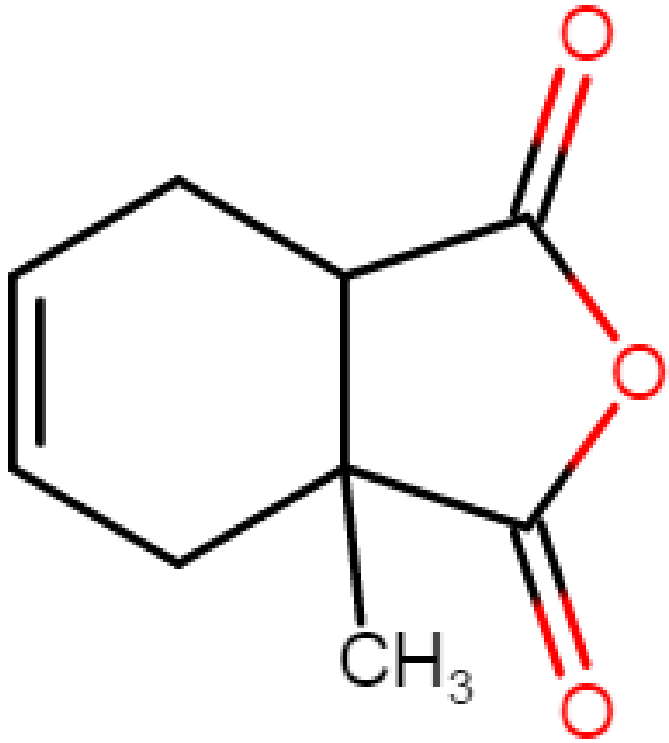
Structural Formula	

	
Molecular Formula	C9H10O3
Molecular Weight	166.18

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