Hexahydromethylphthalic anhydride (MHHPA): Human health tier II assessment

30 June 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,3-Isobenzofurandione, hexahydro-5-methyl-	19438-60-9
1,3-Isobenzofurandione, hexahydro-4-methyl-	57110-29-9

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 listed on the Australian Inventory of Chemicals (AICS), hexahydro-4-methylphthalic anhydride (4-MHHPA) (CAS No. 19438-60-9) and hexahydro-3-methylphthalic anhydride (3-MHHPA) (CAS No. 57110-29-9) are representative of 'hexahydromethylphthalic anhydride' (MHHPA); where *cis*- and *trans*- stereoisomeric forms or 'any combination (reaction mass or unknown or variable composition, complex reaction products and biological materials (UVCB) substance)' are captured under this group definition. Thus the description MHHPA also covers the following chemicals (not on the AICS):

- the UVCB, hexahydromethylphthalic anhydride (MHHPA) (CAS No. 25550-51-0);
- the isomer, hexahydro-1-methylphthalic anhydride (1-MHHPA) (CAS No. 48122-14-1) (ECHA, 2012).

The uses of the chemicals and their hazardous properties (potency for skin and respiratory sensitisation) are expected to be driven by the acid anhydride functional group (ECHA, 2012). Animal and human data from other structurally-relevant cyclic acid anhydrides (on the AICS) including hexahydrophthalic anhydride (HHPA) (CAS No. 85-42-7) and to a lesser extent, trimellitic anhydride (TMA) (CAS No. 552-30-7) are considered relevant analogues (NICNASa; NICNASb), and will be used for read-across when 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; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database and the European Chemicals Agency (ECHA) Annex XV–Substances of Very High Concern (SVHC) dossier.

In general, organic acid anhydrides are commercially available at high purity as liquids or crystals (dependent on the type of 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 % methyl tetrahydrophthalic anhydride (MTHPA) (ECHA, 2012; NICNASa).

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; NICNASa).

The chemicals have reported domestic uses, including in:

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

The domestic uses in adhesives; and paints, lacquers and varnishes were only listed in the SPIN database. It should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that are produced from chemical reactions involving the chemical. The chemicals were not listed on the United States (US) Department of Health and Human Services, Household Products Database, indicating that the chemical is not likely to be widely available for domestic uses.

The chemicals have reported commercial uses, including:

- as fixing agents;
- in viscosity adjusters;
- in construction materials;
- in insulating materials;
- in the manufacture of epoxy resins (as a hardener); and
- in heat transferring agents.

The chemicals have reported site-limited uses, including:

- as chemical intermediates, e.g. in the manufacture of other chemicals.

Restrictions

Australian

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

No known international restrictions have been identified.

The chemical is on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV. In the EU, companies could have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles. The reason for inclusion is based on the respiratory sensitisation hazard as an "equivalent level of concern" (ECHA, 2012).

Existing Worker Health and Safety Controls

Hazard Classification

All the chemicals (under the description MHHPA) are classified as hazardous, with 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

No international exposure standards are available.

Health Hazard Information

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

Toxicokinetics

No data are available.

Based on available data on HHPA, acid anhydrides hydrolyse rapidly and are expected to be the diacid hydrolysis product when present in the systemic circulation. HPPA is readily absorbed following respiratory exposure and can be found in the plasma after absorption, with excretion through the urine (NICNASa).

Acute Toxicity

Oral

Based on data available on hexahydro-4-methylphthalic anhydride (4-MHHPA) and for the analogues hexahydrophthalic anhydride (HHPA) and trimellitic anhydride (TMA), 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 female Sprague Dawley (SD) rats exposed to 4-MHHPA. No treatment-related effects were reported (REACHa; REACHb).

HHPA and TMA also have low acute toxicity by the oral route (LD50 values >2000 mg/kg bw in rats) (NICNASa; NICNASb).

Dermal

No data are available for the chemicals. Based on the available data for the analogues HHPA and TMA, the chemicals are considered to have low acute dermal toxicity.

HHPA and TMA also have low acute toxicity by the dermal route (LD50 values >2000 mg/kg bw in rabbits and rats) (NICNASa; NICNASb).

Inhalation

No data are available for the chemicals. Based on the available data for the analogues HHPA and TMA, the chemicals are considered to have low acute inhalation toxicity.

HHPA and TMA also have low acute toxicity by the inhalation route (LD50 values >1100 and >2330 mg/m^3 in rats, respectively) following four hours of exposure (NICNASa; NICNASb).

Corrosion / Irritation

Skin Irritation

Based on data available on MHHPA (unspecified CAS No.) and analogues HHPA and TMA, the chemicals are considered to be moderately irritating to the skin but classification is not warranted.

In a non-guideline study, MHHPA (0.5 mL; unspecified purity as a liquid) was applied to the abraded and intact skin of six male albino rabbits for 24 hours, under an occlusive patch. Animals were observed at 24 and 72 hours after the patch was removed. The mean erythema Draize scores (24–72 hours) for intact and abraded skin were reported to be 2.00 and 2.33, respectively. The mean oedema Draize scores (24–72 hours) for intact and abraded skin were reported to be 2.25 and 2.67, respectively (REACHa; REACHb).

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) after 24 hours of exposure. Irritation effects were reported to be reversible after 72 hours. No Draize scores were available (NICNASa).

Mild skin irritation was reported in a non-guideline study following a four-hour exposure, after 500 mg of TMA was applied to rabbit skin. Irritation effects were reported to be reversible within the 14-day observation period (NICNASb).

Eye Irritation

No data are available for the chemicals. However, based on the available data for the analogues HHPA and TMA, the chemicals are considered to be severe eye irritants.

In two eye irritation studies, HHPA caused severe irritation to corrosion (irreversible) effects to the washed and unwashed eyes of rabbits (New Zealand White (NZW) rabbits; and in an unspecified strain). No Draize scores were available for the first study but irreversible effects were reported in rabbits (unwashed and washed after 30 seconds, on day 21 post-exposure). Effects was

reported to be reversible by day 19 in eyes rinsed after four seconds. Irreversible effects were reported in the second study. All animals from the unwashed group showed conjunctival effects (mean scores (24, 48 and 72 hours for each animal) chemosis 2, 3, and 2.3; redness 3, 3, and 3), iridial effects (mean score of 1 for all animals) and corneal effects (mean score of 1, 1 and 1.3). Animals with eyes washed after 30 seconds also showed conjunctival effects (mean scores (24, 48 and 72 hours for each animal) chemosis 2.3, 2.3 and 1.7; redness 3, 3, and 3) and corneal effects (mean score of 1 for all animals) (NICNASa).

Eye irritation was reported in a non-guideline study, following application of TMA to rabbit eyes. A maximum Draize score of 110/110 was reported post 24-hours of exposure (NICNASb).

Observation in humans

Based on the available animal data and human observations, the chemicals are considered to be moderate skin irritants.

In a case study, three workers had nasal and/or skin complaints following exposure to MHHPA and HHPA. An irritation reaction (symptoms of nasal pain and rhinorrhoea) was reported in one worker (Yokota et al, 2001).

Sensitisation

Respiratory Sensitisation

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

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 its molecular structure 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 sulphur 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.

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 (NICNASa).

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

Mice (unspecified strain) exposed to HHPA for three days had a T cell response (type 2, T-helper, cytokine secretion), consistent with an allergic respiratory response (NICNASa).

The ECHA (2012) reports MHHPA to be compared to non-threshold carcinogens when respiratory sensitisation is difficult to establish what the threshold dose is for the induction and elicitation phases of response, equivalent to CMR (cat 1 or 2) substances. However, the exposure controls due to the respiratory sensitisation classification are expected to be sufficient to protect workers from any potential systemic effects (refer to **Occupational Risk Characterisation** section).

Skin Sensitisation

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

HHPA (unspecified concentration) was reported to be skin sensitiser based on a guinea pig maximisation test (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 (such as concentration of HPPA used for testing) were available (NICNASa).

TMA was reported to be potentially sensitising to the skin of guinea pigs and rodents. The presence of a solvent increased the dermal sensitisation potential of the chemical (NICNASb).

Observation in humans

MHHPA and other organic acid anhydrides (including HHPA and TMA) can cause respiratory sensitisation and/or skin sensitisation in humans. There are a number of documented case studies of workers exposed to the chemicals and immunological investigations have been reported.

In a case study of three workers with nasal and/or skin complaints who had been exposed to MHHPA and HHPA, the symptoms in one 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 symptoms of 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 (attributed 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 (RAST) (which screens for IgE mediated allergy). Workers also had decreased nasal inspiratory peak flow and an increase in 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 one dermal 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).

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). 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 tested positive for sensitisation to MTHPA in the follow up study (ECHA, 2012; NICNASa).

TMA was reported to cause respiratory sensitisation based evidence from repeat dose inhalation studies (refer to **Repeated Dose Toxicity: Inhalation** section) and in six 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 (NICNASb).

Repeated Dose Toxicity

Oral

No data are available for the chemicals. Based on the limited data for the analogues HHPA and TMA, the chemicals are not considered to cause adverse health effects following repeated oral exposure.

In a 28-day oral gavage study (Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 407), the chemical HHPA was not considered to cause severe systemic toxicity in Charles River (CD-1) rats (n = 5/sex/dose) following repeated oral exposure up to 300 mg/kg bw/day. The majority of treatment-related effects observed were consistent with irritant effects. Treatment-related signs of toxicity (mortality, chin rubbing, salivation and respiratory impairment associated with inflammatory cells in the epithelium of nasal turbinates) were observed at the highest dose (100 mg/kg bw/day). A no observed adverse effect level (NOAEL) of 100 mg/kg bw/day was reported based on local effects (stomach changes, including epithelial hyperplasia in the foveolar region; and respiratory impairment, including submucosal inflammation of the glandular region). In addition, a NOAEL of 300 mg/kg bw/day was reported for systemic effects (no systemic effects at highest dose) (NICNASa).

In chronic oral studies in rats and dogs, TMA was reported to not cause any treatment-related effects following repeated oral exposure (NOAELs of 500 mg/kg day/bw were identified) (NICNASb).

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 six hours/day, five 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.(NICNASb).

Genotoxicity

Based on the available in vitro data on 4-MHHPA, 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 studies, several in vitro assays using 4-MHHPA gave generally negative results in (REACHa; REACHb):

- 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 a bacterial reverse mutation assays in *Escherichia coli* (WP2uvrA) strains, with or without metabolic activation at concentrations up to 5000 µg/plate;
- positive results in a chromosomal aberration assay in human lymphocyte cells, with or without metabolic activation at concentrations up to 1680 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 1800 µg/mL.

The chemical structures did not have 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.

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 (NICNASa; NICNASb).

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

No data are available for the chemicals. Based on the limited data from the analogues HHPA and TMA, the chemicals are not expected to cause specific reproductive or developmental toxicity effects.

In a combined repeated dose reproductive developmental toxicity screening test (OECD TG 421), SD rats (n = 10/sex/dose) that were administered HPPA by oral gavage did not cause any treatment-related adverse effects on reproductive or developmental parameters at doses up to 1000 mg/kg bw/day (NICNASa).

TMA was considered to not cause reproductive or developmental toxicity in rats and guinea pigs following chronic exposure to concentrations of 0.5 mg/m^3. No histopathological effects on reproductive tissues were reported in other subchronic oral and inhalation exposure studies in rats and dogs at doses of 500 mg/kg bw/day (NICNASb).

Risk Characterisation

Critical Health Effects

The critical health effect 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). The relevance of the potential domestic uses are unclear and the chemicals are expected to be used in the manufacture of other chemicals for these uses (and may not be present in the finished products).

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 result in an increased risk of developing respiratory allergy (ECHA, 2012). However, 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 both 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 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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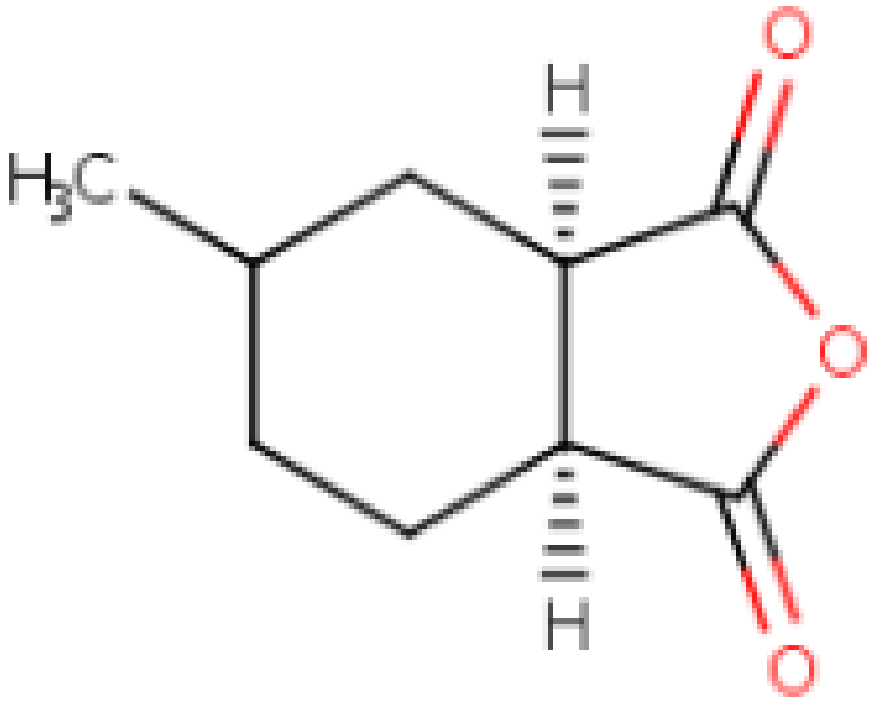
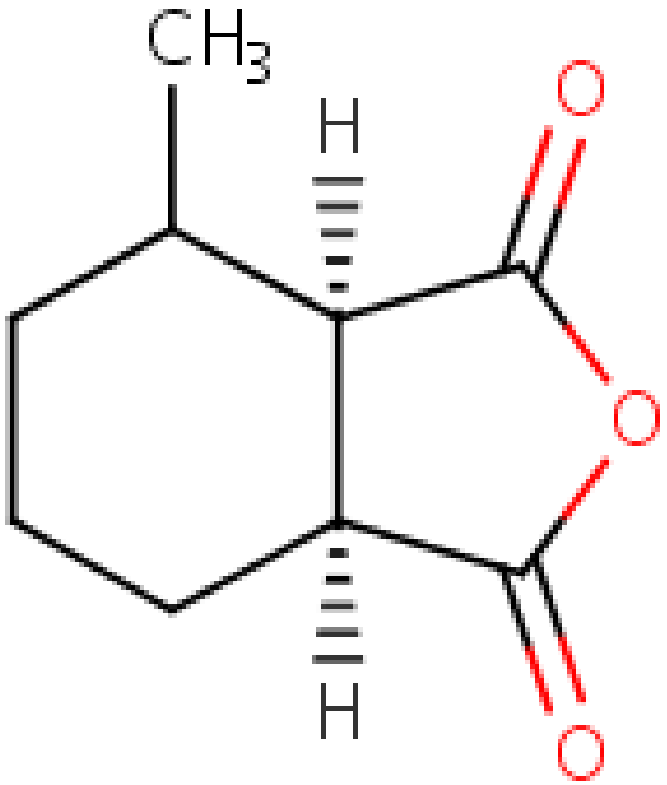
Last Update 30 June 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, hexahydro-5-methyl-** hexahydro-4-methylphthalic anhydride (4-MHHPA) 4-methylcyclohexyl-1,6-dicarboxylic acid anhydride 1,2-cyclohexanedicarboxylic anhydride, 4-methyl- 5-methylhexahydrophthalic anhydride 4-methyl-1,2-cyclohexanedicarboxylic anhydride
CAS Number	19438-60-9
Structural Formula	

	
Molecular Formula	C9H12O3
Molecular Weight	168.19

Chemical Name in the Inventory and Synonyms	**1,3-Isobenzofurandione, hexahydro-4-methyl-** hexahydro-3-methylphthalic anhydride (3-MHHPA) 3-methylhexahydrophthalic anhydride 1,3-isobenzofurandione, hexahydro-4-methyl-
CAS Number	57110-29-9
Structural Formula	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