2,4-Pentanedione: Human health tier II assessment

26 October 2018

CAS Number: 123-54-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

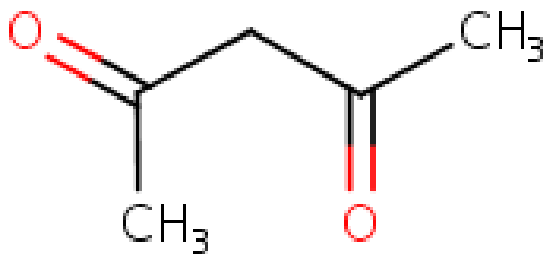
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	acetylacetone 2,4-dioxopentane acetyl 2-propanone
Structural Formula	
Molecular Formula	C5H8O2
Molecular Weight (g/mol)	100.12
Appearance and Odour (where available)	Colourless to pale yellow clear liquid
SMILES	C(C)(=O)CC(C)=O

Import, Manufacture and Use

Australian

The chemical has reported commercial and domestic uses as a thinner in automotive paints.

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD) Screening information data set International Assessment Report (SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic use, including in cleaning and washing agents.

The chemical has reported commercial use, including:

- as a solvent;
- as a fixing agent;
- as an accelerator;
- in paints, lacquers and varnishes (to promote drying);
- as a fuel additive;
- as a defoaming agent; and
- in surface coatings.

The chemical has reported site-limited use, including:

- as an intermediate in the manufacture of dyes;
- in the production of plastics;
- as an intermediate for resin additives; and
- in catalyst systems for the polymerisation of olefins for the control of curing rates in polyurethane coatings.

The chemical has reported non-industrial use, including as an intermediate in the manufacture of pharmaceuticals and pesticides.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Acute toxicity – Category 4; H302 (Harmful if swallowed).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 83–104 mg/m^3 (20–25 ppm) time weighted average in Germany, Spain, Switzerland and the USA, and 166 mg/m^3 (40 ppm) short-term exposure limit in Spain and Switzerland.

Health Hazard Information

Acetylacetone (CAS No. 123-54-6) is an organic compound that exists in 2 tautomeric forms that interconvert rapidly and are treated as a single compound in most applications. The chemical has a range of industrial uses in domestic, commercial and site-limited applications. 2,4-Pentanedione cadmium derivative (CAS No. 14689-45-3) has previously been assessed by NICNAS; however, as cadmium is the driver of toxicity related to this compound, data are not able to be read-across for the assessment acetylacetone (NICNAS).

Toxicokinetics

A toxicokinetic study was conducted in male Fischer 344 (F344) rats. The chemical was shown to be rapidly absorbed via the inhalation route following exposure to radiolabelled ^{14}C-labelled acetylacetone at 400 ppm via nose-only inhalation for 6 hours. There was a rapid increase in plasma radioactivity during the first 3 hours of exposure, with a tendency to plateau toward the end of the 6 hour exposure period. Immediately post exposure, radioactivity was present in all tissues examined. There was no preferential distribution of the chemical in any organ. Plasma concentrations of the unmetabolised chemical declined rapidly to undetectable levels by 12 hours post exposure. Over 48 hours, the percentage of chemical excreted in urine and exhaled breath was 37.6 % and 36.3 %, respectively. Chromatographic data from this study indicates that relatively little of the absorbed chemical remains unchanged before being excreted. Animals were also dosed with the chemical via intravenous injection. Linear kinetics were demonstrated. The chemical was similarly distributed and absorbed following injection compared with the inhalation studies. Across both sets of experiments, 7 metabolic products were identified, but specific metabolites were not reported. By virtue of their presence in urine, the metabolites were considered to be water-soluble and more polar than their parent compound (OECD SIAR, 2001; REACH).

Acute Toxicity

Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful if swallowed’ (H302) in the HCIS (Safe Work Australia). The available data support this classification.

A study was conducted similar to OECD Test Guideline (TG) 401 (acute oral toxicity) to assess the acute oral toxicity of acetylacetone in Wistar rats. Males and females (5/dose) were administered the chemical via oral gavage at 0, 0.25, 0.50, 0.71 and 1 mL/kg body weight (bw). Mortalities were: 1/5, 5/5 males in the 0.71 and 1 mL/kg bw groups, respectively, and 5/5 females in both the 0.71 and 1 mL/kg bw groups. Signs of toxicity included sluggishness, tremors, kyphosis, lacrimation, unsteady gait, comatose appearance and prostration. Survivors recovered 1 to 2 days following dosing. On the basis of these findings, the investigators reported acute median lethal dose (LD50) values of 0.76 and 0.57 mL/kg bw (equivalent to 741 and 556 mg/kg bw when adjusted for density, respectively) for males and females, respectively (OECD SIAR, 2001; REACH).

Dermal

The chemical has moderate acute toxicity based on results from an animal test following dermal exposure. The LD50 in rabbits was 790 mg/kg bw for males, and 1370 mg/kg bw for females. Hazard classification is recommended (see **Recommendation** section).

A non-guideline study was conducted in accordance with good laboratory practice to assess the acute dermal toxicity of acetylacetone in New Zealand White (NZW) rabbits. The test chemical was topically administered to 5 animals of each sex at 0.5, 1 or 2.0 mL/kg bw on the clipped intact skin, under occlusive conditions. Mortalities in these groups were: 0/10, 5/10 and 9/10, respectively. Necroscopic examination of deceased animals revealed red mottled lungs and congestion of the tracheal mucosa. Effects at the site of application included erythema, oedema, scab formation and necrosis. On the basis of these findings, the LD50 for dermal acute toxicity was 790 mg/kg bw and 1370 mg/kg bw for males and females, respectively (Ballantyne et al., 1986).

Inhalation

The chemical has moderate acute toxicity based on results from an animal test following inhalation exposure. The median lethal concentration (LC50) in rats is 4664 mg/m^3 (equivalent to 4.66 mg/L). Hazard classification is recommended (see **Recommendation** section).

Acetylacetone was assessed in a study conducted according to OECD TG 403 (acute inhalation toxicity). Wistar rats of both sexes (10/dose) were inhalationally exposed to the vapour of the chemical (whole body system) for 4 hours at 0, 628, 919, 1231 or 1508 ppm (corresponding to 0, 2619, 3823, 5133 and 6288 mg/m^3). Mortalities for these groups were 0/5, 0/5, 0/5, 5/5, 3/5, and 0/5, 0/5, 0/5, 1/5, 5/5 for males and females, respectively. Signs of toxicity included reduced reflexes, respiratory difficulties, tremors as well as periocular, perioral and perinasal wetness and encrustation. On the basis of these findings, the LC50 was 1224 ppm (equivalent to 4.66 mg/L) (Ballantyne et al., 1986).

In a study conducted according to OECD TG 403, F344 rats (10/sex/dose) were inhalationally exposed to the chemical vapour (whole body system) for 4 hours at 1225 and 18800 ppm. Mortalities for these groups were 2/10 males in the low dose group, and 6/10 and 8/10 males and females from the high dose group, respectively. Clinical signs were eye lid spasms, lacrimation, laboured breathing, urogenital wetness, decreased activity as well as perioral and perinasal encrustation. Surviving animals showed significantly reduced weight gain at both doses. Due to the study design, an LC50 could not readily be established (REACH).

Observation in humans

Inhalational exposure to acetylacetone vapour in humans has been reported to cause non-specific effects such as dizziness, headache, nausea, vomiting and loss of consciousness (OECD SIAR, 2001).

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate skin in an animal study. The effects were not sufficient to warrant hazard classification.

The potential for acetylacetone to produce skin irritation was assessed in a study similar to OECD TG 404 (acute dermal irritation/corrosion). The clipped, intact skin of NZW rabbits (3/sex) was topically treated with 0.5 mL of undiluted test material under occlusive conditions. The dressings were removed after 4 hours and the sites of application were assessed for signs of irritation/corrosion. Treated skin areas were inspected 1 hour and 1, 2, 3, 7 and 14 days after removal of the dressing. After 1 hour, slight erythema was observed in 5/6 animals and moderate oedema was observed in 1/6 animals. After 48 and 72 hours, 5 and 3 animals showed very mild erythema, respectively. Mild oedema was observable at 48 and 72, hours in 2 and 1 animals, respectively. The chemical was found to be slightly irritating under these conditions (Ballantyne et al., 1986).

Eye Irritation

The chemical is reported to be a mild eye irritant in animal studies. The chemical is reported to be an eye irritant in in vitro assays. Based on the weight of evidence, the effects of the chemical were not considered sufficient to warrant hazard classification.

Acetylacetone was assessed for its potential to produced ocular irritation in a study conducted similarly to OECD TG 405 (acute eye irritation/corrosion). The undiluted chemical (0.1 mL) was instilled into the conjunctival sac of 1 eye in each of 6 female NZW rabbits, and the eyelids held closed for 1 second. The eyes were not washed and animals were observed for 14 days post treatment. Corneal opacity was not observed at any time point. Slight redness of the conjunctivae was observed in 5/6 animals after 1 hour. Slight and moderate chemosis was observed in 2/6 and 1/6 animals, respectively. Slight and moderate discharge was observed in 2/6 and 3/6 animals, respectively, and slight iridial inflammation was observed in 2/6 animals. All irritative effects were fully reversed after 24 hours. On the basis of these effects, the chemical was found to be slightly irritating (Ballantyne et al., 1986).

The chemical was assessed in an eye irritation study conducted similarly to OECD TG 405. Undiluted acetylacetone (0.5 mL) was applied to 1 eye in each of 3 rabbits (strain not specified). Eyes were washed after 1 hour and animals were observed for 21 days. Few experimental details are available; however, the investigators reported that the chemical was slightly irritating to the eyes (OECD SIAR, 2001).

A multinational, inter-laboratory study in 12 European laboratories using the in vitro bovine corneal opacity and permeability (BCOP) assay has been conducted using acetylacetone. In this assay, bovine corneas, harvested from recently deceased animals were incubated with undiluted acetylacetone for 10 minutes. Measurements of opacity with and without fluorescein staining was performed immediately after removing of the test substance and then again 2 hours after. The following scoring classification system applies: a score of 0–25 is considered a mild irritant; 25.1–55, a moderate irritant and a score of 55.1 or higher, a severe irritant. The mean score from studies from 12 laboratories was found to be 59.8 (individual scores 34–79). On the basis of this finding, the chemical was considered to be a severe irritant according to the BOCP test. However, when the BCOP test method is used to identify chemicals inducing serious eye damage (as defined by the Globally Harmonised System for the Classification of Chemicals (GHS)), it has a false positive rate of 25 % when compared to in vivo rabbit eye test method data. The false positive rate for ketones is particularly high (OECD, 2013).

Observation in humans

There are reports of the chemical causing mild, reversible dermal and ocular irritation in humans (OECD SIAR, 2001).

Sensitisation

Skin Sensitisation

The negative results observed for the chemical in 2 animal studies support a conclusion that the chemical is not a skin sensitiser.

Acetylacetone was assessed in a skin sensitisation study according to OECD TG 429 (skin sensitisation: local lymph node assay). Female CBA mice (5/dose) were topically administered the chemical at 12.5, 25 or 50 % (in acetone/olive oil (4:1 v/v)) to the entire dorsal surface of each ear, once daily over 3 consecutive days. None of the 3 tested concentrations produced a stimulation index of 3 and; therefore, the investigators determined that the chemical was not a skin sensitiser in this test system (REACH).

A skin sensitisation study was conducted with acetylacetone in guinea pigs; however, very few experimental details are available. Five guinea pigs were treated on the basis of a standardised skin sensitisation test (details not available) and 1/5 guinea pigs showed a weak response. The remaining 4/5 animals showed no evidence of sensitisation. The study authors indicated that this was an ambiguous finding (OECD SIAR, 2001).

Observation in humans

Acetylacetone was assessed in a human skin sensitisation patch test in 12 volunteers. No information was available concerning the gender, health status or predisposition to allergic reactions of the volunteers. Of the 12 persons tested, 3 showed no response, 7 showed doubtful responses and 2 showed positive reactions after an exposure period of 24 hours. No skin reactions were evident after 48 and 72 hours. The results observed in the human patch test were interpreted as irritating rather than sensitising. The results of this study are difficult to interpret given the lack of details available (Sterry & Schmoll, 1985).

Repeated Dose Toxicity

Oral

Acetylacetone was assessed in a repeated dose oral toxicity study. Rats of unspecified strain (5/dose) were administered the chemical at 0, 100, 500 or 1000 mg/kg bw/day by oral gavage for 1–15 days (specific details on the dosing regimen not available). All animals in the highest dose group died within 1 hour of receiving the first dose. In the 500 mg/kg bw/day dose group, 3/5 animals died and 2/5 were sacrificed due to poor condition after the fourth administration. Animals were evaluated for a range of parameters (clinical signs, changes to weight gain, changes to organ weights, haematology, clinical chemistry, histopathology, gross pathology and clinical chemistry). Substance-related systemic effects in the 500 mg/kg bw/day dose group included distended bladders, congested lungs, corneal opacity, thymic necrosis, hepatocyte swelling, nephrosis, lymphadenitis of mesenteric lymph nodes and inflammation of the heart. In the 100 mg/kg bw/day group no adverse reactions to dosing were observed in any of the parameters assessed. On the basis of this result, a no observed adverse effect level (NOAEL) of 100 mg/kg bw/day was determined (OECD SIAR, 2001).

Dermal

The potential for acetylacetone to produced toxicity following repeated dermal applications was investigated in a non-guideline study. NZW rabbits were topically administered the chemical at 0.25, 1.0 or 1.5 mL/kg bw/day (equivalent to 244, 975 and 1463 mg/kg bw/day, respectively) under occlusive conditions for 6 hours per application. The test substance was applied to the clipped dorsal skin of the rabbits (12/sex/group for the high dose group and 6/sex/group in the mid and low dose groups). The original study design required dosing for 5 days in the first week and dosing for 4 days in the second week. The dosing regimen was only able to be completed for the low dose group. Dosing was discontinued for the mid and high dose groups after day 4 of the experiment due to mortalities and signs of toxicity. Mortalities in these groups were 5/12 males and 7/12 females in the 1.5 mL/kg (1463 mg/kg) group and 1/6 males and 3/6 females in the 1.0 mL/kg (975 mg/kg) group. Mid and high dose group

animals exhibited signs of systemic toxicity including hypoactivity, discoordination, tremors, excessive salivation, gasping and/or convulsions and showed evidence of cyanosis. Reduced body weight gain and decreased food consumption compared with control animals were also observed during the first few days of the study. In the low dose group there were no mortalities, clinical signs of systemic toxicity, or effects on body weight or food consumption. At necropsy, brain pathologies were observed in the high and mid dose group including haemorrhage and neuronal degeneration. Lymphoid organ congestion and haemorrhage were also observed in these animals. Severe skin irritation was observed at the sites of application in all animals in all dose groups. The time of onset and severity of irritation were dose-dependent. Signs of irritation included erythema, oedema, desquamation, excoriation, fissuring, necrosis and/or ecchymosis. Gross and microscopic evaluation at both day 4 and 12 confirmed dose-related skin irritation in all treatment groups. Microscopic lesions included acanthosis, subcutaneous oedema, dermatitis, haemorrhage, congestion and/or necrosis. The particularly severe signs of irritation were reported to be at least in part due to the occlusive conditions for application used in the study. On the basis of the systemic effects observed in this study, the investigators reported an NOAEL of 244 mg/kg bw/day (REACH).

Inhalation

The chemical was assessed in a repeated dose inhalation toxicity study in F344 mice. Animals (20/sex/group) were exposed to acetylacetone vapour at 0, 100, 300 or 650 ppm (corresponding to 0, 417, 1217 and 2711 mg/m^3, respectively) for 6 hours/day, 5 days/week for 14 weeks. In the highest dose group, all females died during the second week, and a third of all males died in the sixth week. Animals in this group exhibited lacrimation, ataxia, hypoactivity and hypothermia. Surviving animals in this group showed decreased body weight gains, decreased absolute organ weights although often increased relative to body weight, and minor alterations in haematology, serum and urine chemistry. Thymus and brain degeneration was observed in surviving animals. In the mid dose group, there were minor alterations in haematology, serum and urine chemistry. The mid dose females also showed slight decreases in body weight gains compared with controls. Effects were fully reversed in the 4 week period post-dosing. In the low dose, there were no substance-related deaths. There were no observed changes in clinical signs, serum or urine chemistry, haematology or histopathology. On the basis of these effects, a no observed adverse effect concentration (NOAEC) of 300 ppm (equivalent to 1217 mg/m^3/6 hours/day) was determined for acetylacetone following repeated inhalational exposures in F344 mice. This was calculated to be equivalent to an NOAEL of 144.1 mg/kg bw/day, assuming a respiratory minute volume of 0.24 L/min (14.4 L/h) and an average weight of 250 g/rat (OECD SIAR, 2001; REACH).

Acetylacetone was assessed in a repeated dose inhalation toxicity study. F344 rats (10/sex/dose) were exposed to the vapour of the chemical at 0, 197, 418 or 805 ppm (equivalent to 0, 834, 1668 and 3336 mg/m^3) (whole body exposure system), for 6 hours per day for 9 days (with a 2 day period of no exposures after 5 days). No animals died during the study. Transient body weight loss was observed during the first week of exposure in animals in the high dose group. Reduced body weight gain was observed during the first week of exposure in both sexes in the high dose group and in male rats in the mid dose group; no body weight changes were observed in the 200 ppm dose groups. Organ weights were reduced in the high dose group. No organ weight changes were observed in the low dose group. There was generalised leucocytosis in both sexes in the high dose group (including an increase in lymphocyte numbers). No haematological changes were observed in the mid and low dose groups. Exposure-related inflammation of the nasal mucosa was observed in all exposed rats; necrosis of the nasal mucosa was observed in the high dose group and occasionally in the mid dose group. Mild inflammation of the larynx was observed in 2 males in the high dose group. No lower respiratory tract lesions were observed in any animal. Mild vacuolisation of the brain stem was observed in 2 animals in the high dose group. On the basis of these findings, the investigators reported an NOAEC of 834 mg/m^3/6 hours/day (REACH).

Genotoxicity

Based on the weight of evidence from the available well-conducted in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic. Although the chemical produced positive results in some in vitro assays, most in vivo studies were negative.

In vitro

An Ames test was conducted according to OECD TG 471 (bacterial reverse mutation assay). Acetylacetone was found to be negative for genotoxicity when tested at 0.3, 1, 3, 10 or 30 mg/plate in *Salmonella typhimurium* strains TA 98, TA100, TA1535, TA1537 and TA1538, both in the absence and presence of metabolic activation (REACH).

An Ames test was conducted similar to OECD TG 471. Acetylacetone was incubated with *S. typhimurium* strains TA92, TA98, TA100 and TA104 in the absence of metabolic activation. No information was available with regard to the concentration ranges of the test chemical used in strains TA92, TA98 and TA100, where no mutagenic effects were reported. Test concentrations incubated with the TA104 strain were 1.9–48 µmol/plate (in 0.1 mL total volume added per plate). The chemical was considered only slightly mutagenic in TA104 at concentrations ranging from 1.9–10 µmol/plate. At concentrations higher than 10 µmol/plate, there were no statistically significant increases in the number of revertant colonies. Therefore, the increase of revertant colonies/plate was not dose-dependent, and the chemical could not definitively be considered to be mutagenic (OECD SIAR, 2001).

The chemical was assessed in a study conducted similar to OECD TG 479 (genetic toxicology: in vitro sister chromatid exchange (SCE) assay in mammalian cells). Chinese hamster ovary (CHO) cells were incubated with acetylacetone for 5 hours at 0.02–0.1 mg/mL (without metabolic activation) and at 0.03–0.3 mg/ mL (with metabolic activation). Investigators reported a statistically significant increase in the number of SCEs in the 3 highest doses in the absence of metabolic activation. The 0.1 mg/mL dose produced a statistically significant increase in SCEs (which was greater than that observed with a comparable concentration of the positive control). The chemical was also found to significantly increase the number of SCEs in the presence of metabolic activation. In this test system, the chemical was considered to be a potent genotoxin (OECD SIAR, 2001; REACH).

The chemical was assessed in a study conducted similar to OECD TG 476 (in vitro mammalian cell gene mutation test). CHO cells were exposed to acetylacetone for 5 hours at 0.005–1.5 mg/mL (without metabolic activation) and at 0.005–1.0 mg/mL (with metabolic activation). The test chemical did not produce any statistically significant increases in the incidence of mutations in CHO cells at any concentration tested, either in the absence or presence of metabolic activation. Therefore, the chemical was considered to be negative for genotoxicity under these test conditions (OECD SIAR, 2001; REACH).

The chemical was assessed in a study conducted similar to OECD TG 473 (in vitro chromosome aberration test). CHO cells were exposed to acetylacetone for 6 hours at 0.04–0.12 mg/mL (without metabolic activation) and at 0.06–0.14 mg/mL (with metabolic activation). In tests performed without metabolic activation, all 3 of the dose levels produced significant increases in numbers of chromosome aberrations. There were no significant increases in the number of chromosome aberrations when CHO cells were incubated with the test chemical in the presence of metabolic activation. Therefore, the chemical was considered to be clastogenic under the conditions of this test system (REACH).

In vivo

The chemical was assessed in a study conducted similar to OECD TG 474 (mammalian erythrocyte micronucleus test). Swiss Webster mice (5/sex in the low and mid groups; and 7/sex in the high dose group) were exposed to acetylacetone vapour at 0, 100, 400 and 600 ppm (whole body exposure). Animals were exposed for 6 hours/day for 5 consecutive days. The chemical did not produce significant or dose-dependent increases in the frequency of micronucleated polychromatic erythrocytes (PCEs) in the bone marrow harvested from exposed animals. The chemical was considered not to be genotoxic under these test conditions (OECD SIAR, 2001; REACH).

The chemical was assessed in a study conducted similar to OECD TG 474 (mammalian erythrocyte micronucleus test). Sprague Dawley (SD) rats (5/sex/dose) were exposed to acetylacetone vapour at 0, 100, 400 and 600 ppm (whole body exposure). Animals were exposed for 6 hours/day for 5 consecutive days. Acetylacetone produced a statistically significant increase in the incidence of chromosomal aberrations in the bone marrow of 1 rat exposed at 100 ppm. However, there was no dose-dependent response as the chemical did not produce statistically significant increases in the frequency of micronucleated PCEs in the other dose groups. The chemical was considered not to be genotoxic under these test conditions (OECD SIAR, 2001; REACH).

A study was conducted to assess the potential for acetylacetone to induce micronuclei formation in Swiss Webster mice following intraperitoneal injection. Animals (5/sex/dose) were administered the chemical at 0, 200, 400 and 650 mg/kg bw. Blood samples were collected 0, 48 and 72 hours after injection, and micronucleated PCEs were analysed. At 30 and 48 hours, a statistically significant increase in the number of micronucleated PCEs was detectable in a dose-dependent manner while there was no difference in the number of PCEs with micronuclei in blood samples collected after 72 hours, compared with controls. On the basis of these findings, the investigators reported that the chemical was genotoxic following intraperitoneal injection (OECD SIAR, 2001).

A study was conducted to assess the potential for acetylacetone to induce micronuclei formation in SD rats following intraperitoneal injection. Animals (5/sex/dose) were administered the chemical at 0, 50, 100, 200, 400 and 650 mg/kg bw. Blood was collected for the analysis of PCEs for the presence of micronucleus formation. No statistically significant treatment-related increases in the incidence of micronucleated PCEs were observed (OECD SIAR, 2001).

A comet assay was conducted on acetylacetone. Male Wistar rats (7/animals/dose) were administered the chemical via oral gavage at 0, 400 and 800 mg/kg bw. Animals were administered the chemical twice (24 and 4 hours prior to animal sacrifice and harvest of liver and small intestine cells). Investigators reported that the chemical did not induce any DNA damage at any of the doses tested. On the basis of these findings, the chemical was not considered to be genotoxic in this test system (REACH).

The potential for acetylacetone to induce germ cell mutations was assessed in a non-guideline dominant lethal assay in male F344 rats following inhalational exposure to acetylacetone. Animals (20/group) were exposed to the chemical vapour at 0, 100, 400 and 700 ppm (approximately equivalent to 0, 417, 1668 and 2919 mg/m^3, respectively). The animals were exposed to the test substance for 6 hours per day for 5 consecutive days. Following the last exposure, animals were mated with unexposed females for a period of 8 weeks. In week 3, there was a slight reduction in the number of pregnant females that were mated with males from the two highest dose groups. Gestational parameters were affected in weeks 2 and 4 of mating and characterised by a reduction in the number of corpora lutea per dam in week 2 and a reduction in the number of total and viable implants per dam both in week 2 and 4 at 700 ppm. There was a slight (not statistically significant) increase in post implantation losses at the two highest doses in week 2 and there was a statistically significant increase in preimplantation losses in week 4. There was a high variability in the data generated in this study, and the investigators determined that it was not possible to make a determination of the substance-related dominant lethal effect (Tyl et al., 1989; OECD SIAR, 2001).

A germ cell genotoxicity assay was conducted in NMRI mice. Acetylacetone was administered to 6 male NMRI mice at 800 mg/kg bw via drinking water. Spermatagonia were harvested from animals at 24 or 48 hours after dosing. There was no reduction in mitotic indices or structural chromosomal aberrations in the substance-treated animals compared with controls. Under this test system, the chemical was considered to be non-clastogenic (OECD SIAR, 2001).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

No study has been conducted to assess the potential for acetylacetone to produce reproductive toxicity. However, some data are available from a repeated dose inhalation toxicity study in F344 mice. Animals (20/sex/group) were exposed to acetylacetone vapour at 0, 100, 300 or 650 ppm (corresponding to 0, 417, 1217 and 2711 mg/m^3, respectively) for 6 hours/day, 5 days/week for 14 weeks (see **Repeated Dose Toxicity: Inhalation** for further details). There were no pathological findings of note in the testes or epididymis of any male, or in the uterus, cervix or ovaries of any female. On the basis of these effects, the NOAEL for reproductive toxicity was 650 ppm (equivalent to 2711 mg/m^3) (OECD SIAR, 2001).

A study was conducted to assess the potential for the chemical to cause developmental toxicity according to OECD TG 414 (prenatal developmental toxicity study). Pregnant F344 rats (25/dose) were inhalationally exposed to the chemical vapour on gestational days (GD) 6 to 15 at 0, 52.7, 202 or 398 ppm to evaluate the embryotoxic and fetotoxic (including teratogenic) potential of the administered chemical during organogenesis. Animals were exposed on consecutive days for 6 hours per day. Apart from significantly reduced body weight gain in the 398 ppm exposure group, no treatment related effects on body weights, liver weights, thymus weight and gravid uterine weights were observed in any dose group. No treatment related effects were observed on the number of corpora lutea, on total, non-viable and viable implantations per litter, pre- or post-implantation loss. There were no maternal deaths, early deliveries or abortions. Foetal effects were observed, including a significant reduction in female foetus body weight at the 2 highest doses. There was a consistent pattern of reduced ossification in foetuses from the 398 ppm group (incomplete ossification of the phalanges, cervical vertebrae and thoracic centrum was observed). Investigators reported reduced foetal weights in males at 202 ppm, and in males and females at 398 ppm. On the basis of these effects, the NOAEC was determined to be 52.7 ppm for developmental toxicity. An NOAEC of 200 ppm was determined for maternal toxicity (OECD SIAR, 2001; REACH). The developmental delays seen at the highest concentration are likely to be non-specific responses to maternal ill health.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral/dermal/inhalation exposure).

Public Risk Characterisation

The chemical has reported domestic use overseas as cleaning and washing agents. In Australia, the chemical was reported to have been used as a thinner in commercial and domestic automotive paints.

Provided that normal precautions are taken to avoid prolonged skin and eye contact, the risk to public health posed by the chemical, when used in automotive paints and cleaning products, is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal, oral and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. Oral exposures are usually assumed to be adequately restricted by routine industrial hygiene measures. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2018).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the GHS as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances System.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)* Harmful in contact with skin - Cat. 4 (H312) Toxic if inhaled - Cat. 3 (H331)

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

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

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

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal 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 storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

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

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