Allyl esters of acetic acid ethers: Human health tier II assessment

28 June 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Acetic acid, phenoxy-, 2-propenyl ester	7493-74-5
Acetic acid, (3-methylbutoxy)-, 2-propenyl ester	67634-00-8
Acetic acid, 2-(2-methylbutoxy)-, 2-propenyl ester	67634-01-9
Acetic acid, (cyclohexyloxy)-, 2-propenyl ester	68901-15-5

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 esters of allyl alcohol (CAS No. 107-18-6) and an alkoxycarboxylic acid. They follow a similar metabolic route, i.e., hydrolyse to allyl alcohol followed by metabolism to the reactive acrolein (CAS No. 107-02-8) in the liver. All chemicals in this group are used in food flavouring or as fragrance components.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the majority of the chemicals in this group. However, acetic acid, (3-methylbutoxy)-, 2-propenyl ester (CAS No. 67634-00-8) has reported use in rubber compound and in marine applications.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the European Commission Cosmetic Ingredients and

Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Household Products Database; and the International Fragrance Association (IFRA) Transparency List.

All chemicals in this group have reported cosmetic use in perfumes or as fragrance ingredients.

Allyl phenoxyacetate (CAS No. 7493-74-5), allyl (3-methylbutoxy) acetate (CAS No. 67634-00-8) and allyl cyclohexyloxyacetate (CAS No. 68901-15-5) have reported domestic uses in air fresheners, surface wipes, scented oils and wax and toilet bowl cleaners (Household Products Database; REACHa–c).

Allyl cyclohexyloxyacetate (CAS No. 68901-15-5) has site limited use as an intermediate (Galleria Chemica).

There is currently no documented use of the chemicals in the Compilation of Ingredients used in Cosmetics in the United States (CIUCUS, 2011). All chemicals except allyl (3-methylbutoxy)acetate (CAS No. 67634-00-8) are not on the US Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

All chemicals have reported non-industrial use as food additives.

Restrictions

Australian

Specific allyl esters are listed in Schedule 6 of the *Poison Standard — the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2019) as follows:

Schedule 6:

'ALLYL ESTERS (excluding derivatives) being:

ALLYL CYCLOHEXANEACETATE (CAS No. 4728-82-9)

ALLYL CYCLOHEXANEPROPIONATE (CAS No. 2705-87-5)

ALLYL HEPTANOATE/ALLYL HEPTYLATE (CAS No. 142-19-8)

ALLYL HEXANOATE (CAS No. 123-68-2)

ALLYL ISOVALERATE (CAS No. 2835-39-4)

ALLYL NONANOATE (CAS No. 7493-72-3)

ALLYL OCTANOATE (CAS No. 4230-97-1)

ALLYL PHENYLACETATE (CAS No. 1797-74-6)

ALLYL TRIMETHYLHEXANOATE (CAS No. 68132-80-9)

in preparations containing 0.1 per cent or less of free allyl alcohol by weight of allyl ester **except** in preparations containing 5 per cent of less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl esters' (SUSMP, 2019).'

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label (SUSMP, 2019).

Schedule 7:

'ALLYL ALCOHOL **except**

a) in preparations containing 5 per cent or less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl ester; or

b) when separately specified in these Schedules.'

Schedule 7 chemicals are labelled with 'Dangerous Poison'. These are substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply (SUSMP, 2019).

International

The chemicals are listed in the following (Galleria Chemica):

• EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down (the level of free allyl alcohol in the ester shall be less than 0.1 %); and

• New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

Allyl esters are specified as 'should only be used when the level of free allyl alcohol in the ester is less than 0.1 %. This recommendation is based on the delayed irritant potential of allyl alcohol' (IFRA, 2019).

Allyl phenoxyacetate (CAS No. 7497-74-5) is an IFRA Restricted chemical for sensitisation (IFRA, 2019).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Limited data are available for the chemicals in this group. The chemicals are expected to be hydrolysed in vivo to form the parent alcohol (allyl alcohol) and corresponding acids (NICNASa). Data available (see **Health Hazards** section) for allyl phenoxyacetate indicate that the toxicity effects are expected to be driven by the metabolite, allyl alcohol. Therefore, where available, data from the parent alcohol and the corresponding acids are considered suitable analogues for systemic effects.

Due to structural similarities, the alkoxyethanols including 2-methoxyethanol, 2-ethoxyethanol, and 2-butoxyethanol are considered where necessary for read-across for systemic effects.

Toxicokinetics

There are no toxicokinetic studies for the chemicals in this group. However, based on available toxicity studies in animals, the chemicals can be absorbed via the oral, dermal and inhalation routes, and are predominantly excreted in the urine.

Both allyl phenoxyacetate and allyl cyclohexyoxyacetate are considered to have low bioaccumulation potential based on their log Kow (2.33–2.80). The low molecular weight (MW <500 g/mol) and moderate lipophilicity of these substances also indicate favourable membrane penetration and absorption (REACHa,c).

The metabolism of allyl phenoxyacetate and allyl cyclohexyoxyacetate was predicted using the QSAR OECD toolbox. Hydroxylation and degradation of these substances primarily occurred in the liver and skin. The substances were hydrolysed to allyl alcohol and the corresponding acid (REACHc).

Alkoxyacetic acids are the major metabolites of alkoxyethanols. These were observed to be excreted via the urine more slowly in humans than in animals (NICNASb). The elimination half-life of the acids is dependent on the alkyl chain length, with measured half life for methoxyacetic acid, ethoxyacetic acid and butoxyacetic acid being 77.1 hours, 24 hours and 3.1 hours, respectively. The short-chain acetic acids (methoxy- and ethoxy-) are considered to be responsible for systemic toxicity (reproductive and developmental, and immunotoxicity) associated with these alkoxyethanols, due to relatively slow excretion rates in larger organisms. In contrast, these effects were not observed for the longer chain alkoxy ethers (butyl-, propyl- and phenyl-) (ECETOC, 2014; NICNASc).

In animal studies, phenoxyacetic acid was found to be excreted primarily unchanged in the urine. There was no evidence of conjugation with either glucuronic acid or glycine (JECFA, 2003).

While no data are available for allyl (2-methylbutoxy)acetate, it is expected that its toxicity will be similar to that of its 3-methyl isomer.

Acute Toxicity

Oral

Based on the available data, the chemicals are considered to be acutely toxic and hazard classification is warranted.

The reported median lethal dose (LD50) values in rats are (REACH):

- Allyl phenoxyacetate, 835 mg/kg bw;
- Allyl (3-methylbutoxy)acetate, 500 mg/kg bw; and
- Allyl cyclohexyloxyacetate, 620 mg/kg bw.

Dermal

Based on the available data, the chemicals are considered to have low acute toxicity following dermal exposure.

The reported dermal LD50 values in rats are (REACH):

- Allyl phenoxyacetate, >2000 mg/kg bw;
- Allyl (3-methylbutoxy)acetate, >2000 mg/kg bw; and
- Allyl cyclohexyloxyacetate, >2000 mg/kg bw/day.

Inhalation

Based on the available data for allyl (3-methylbutoxy)acetate, this chemical is considered to be acutely toxic and hazard classification is warranted. No data are available for the other chemicals in this group.

The reported median lethal concentration (LC50) for allyl (3-methylbutoxy)acetate was 0.43 mg/L (4 hour exposure) in rats. Observed sub-clinical signs in the treated rats were clear nasal discharge, ataxia, tremors, salivation, dyspnoea, hypoactivity, and slight piloerection (REACHb).

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemicals in this group are not considered to be strong skin irritants. Therefore, hazard classification is not warranted.

In an acute dermal irritation study (OECD Test Guideline (TG) 404), 0.5 mL of allyl phenoxyacetate (purity not stated) was applied (semi-occluded) to the flank of New Zealand White (NZW) rabbits (n = 4) for 4 hours, with observation up to 7 days. The average scores at 24, 48 and 72 hours were 0.3 for erythema and 0.1 for oedema. The chemical was at most a slight skin irritant (REACHa).

Two skin irritation studies are available for allyl cyclohexyloxyacetate (REACHc).

In an acute dermal irritation study (OECD TG 404), 0.5 mL of allyl cyclohexyloxyacetate was tested (semi-occluded) on the clipped skin of female Himalayan rabbits (n = 4) for 4 hours. The chemical was applied undiluted, and at concentrations of 1, 5, or 25 % in diethyl phthalate. The undiluted chemical caused well-defined erythema in 2 animals and slight erythema in 1 animal at 30 minutes; however, this effect was reversible within 48 hours. No oedema was observed. The individual average scores at 24, 48 and 72 hours were 0.33, 0.33, 0.0, and 0.0 for erythema. The chemical was only slightly irritating to the skin under the conditions of this test.

In a primary skin/corrosion study (OECD TG 404), allyl cyclohexyloxyacetate was applied undiluted, and at concentrations of 1, 5, or 25 % in ethanol on the clipped skin of female Himalayan rabbits (n = 4) for 4 hours, with observation up to 72 hours. Slight erythema was observed in 3 rabbits up to 72 hours, whereupon reversibility was not stated due to termination of the study at 72 hours. The average scores at 24, 48 and 72 hours were 0.83 for erythema and 0.08 for oedema. The chemical was only slightly irritating under the conditions of this study (REACHc).

Eye Irritation

The available information indicates that the chemicals are not strong eye irritants and; therefore, hazard classification is not warranted.

In an eye irritation study (OECD TG 405), allyl phenoxyacetate was instilled into 1 eye of each NZW rabbit (n = 3), with observation up to 7 days. Slight corneal opacity was observed in all animals and slight conjunctival redness in 1 animal. Effects were fully reversible within 2 days. No effects on chemosis or iris effects were observed. The chemical was not considered a strong eye irritant (REACHa)

In an in vitro eye irritation study (OECD TG 437: Bovine Corneal Opacity and Permeability (BCOP) Test), neat allyl cyclohexyloxyacetate (0.75 mL) was applied to the epithelial surface of cattle corneae (n = 3) and incubated for 10 minutes at 32 degrees in a horizontal position. After rinsing with saline, the corneae were incubated for a further 2 hours at 32 degrees in a vertical position. The negative control was 0.9 % (w/v) NaCl solution in deionised water, and the positive control was 2-ethoxyethanol. Relative to the negative control, the chemical did not cause an increase in corneal opacity or permeability. The calculated mean in vitro irritation score (IVIS) was 0.00 (IVIS >55 is regarded as serious eye damage). Therefore, the chemical was not considered to be an eye irritant (REACHc).

QSAR modelling for allyl (3-methylbutoxy)acetate predicted that the chemical was not an eye irritant. The result was in the applicability domain (REACHb).

Sensitisation

Skin Sensitisation

Based on the available animal data, allyl phenoxyacetate is considered a skin sensitiser and classification is warranted. This classification does not apply to the other chemicals in this group.

In a local lymph node assay (LLNA) (OECD TG 429), allyl phenoxyacetate was applied to the ears of female CBA/Ca mice (n = 4/dose) at concentrations of 0.5, 1, 2.5, 5 or 10 % in 1:3 ethanol/diethyl phthalate on 3 consecutive days. The stimulation index (SI) was reported to be 0.8, 1.3, 1.6, 7.5 and 8.1 for the 5 tested concentrations, respectively. The EC3 (effective concentration needed to produce a 3-fold increase in lymphocyte proliferation) value was 3.1 %. There was no increase in skin irritation on or around the ear, apart from day 3 where slight reddening was observed at ≥5 %. This effect was reversible by day 6 (REACHa). Based on the SI values for concentrations at ≥5 % and an EC3 value of ≥1 % to <10 %, the chemical is considered a moderate sensitiser under the conditions of this test.

In a Buehler test (OECD TG 406), male Dunkin-Hartley guinea pigs (n = 20) were topically induced (occlusive) with 100 % allyl cyclohexyloxyacetate for 6 hours, weekly, for 3 applications. On day 28, the animals were challenged with occlusive patches of the chemical at 50 % and 100 % for 6 hours. Observations were made at 24 and 48 hours after challenge patch removal. No positive reactions were observed during induction and after the challenge period. The chemical was not considered to be a skin sensitiser (REACHc)

In a guinea pig maximisation test (GPMT) (OECD TG 406), female Dunkin-Hartley guinea pigs (n = 20) were intradermally induced with 0.05 mL of a solution of 5 % allyl cyclohexyloxyacetate in paraffin oil, followed by topical induction at 100 % concentration 6 days after the injections. The animals were challenged with 0.1 mL of a solution of the chemical in diethyl phthalate at 25 %. The treated sites were evaluated at 24, 48 and 72 hours following exposure. No positive reactions were observed. The chemical was not considered to be a skin sensitiser (REACHc)

QSAR modelling for allyl (3-methylbutoxy)acetate predicted that the chemical was not a skin sensitiser. The result was in the applicability domain (REACHb).

The Scientific Committee on Consumer Safety (SCCS) has categorised allyl phenoxyacetate as an ‘established contact allergen in animals’ (SCCS, 2012).

Repeated Dose Toxicity

Oral

The effects observed for allyl phenoxyacetate suggest that the liver was the primary target organ, consistent with observations for the aliphatic allyl esters and indicates metabolism to allyl alcohol and acrolein (NICNASa). However, the effects observed are not sufficient to warrant hazard classification. In contrast, no adverse effects were observed for allyl (3-methylbutoxy)acetate and allyl cyclohexyoxyacetate up to the highest tested concentrations.

In a combined repeat dose/reproduction and developmental toxicity screening test (OECD TG 422), Sprague Dawley (SD) rats were administered allyl phenoxyacetate at 0, 15, 50 or 150 mg/kg bw/day during the premating period for 14 days, during mating and continued through the day of scheduled sacrifice in males (at least 50 days). Dosing for females continued through gestation and until Day 13 of lactation. No substance-related deaths were observed. At the highest dose, observed effects in both sexes were increases in some haematological parameters (total leukocyte count, absolute lymphocyte count, monocyte count and large unstained cell counts), increases in some clinical chemistry parameters (alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase and total bilirubin), increased liver and spleen weights, and increased testes and epididymides weights. Substance-related effects observed in the liver were cholangiofibrosis, hydropic degeneration and necrosis. In males, increased fibrinogen and platelet count was observed at ≥50 mg/kg bw/day. The no observed adverse effect level (NOAEL) for systemic toxicity was 50 mg/kg bw/day based on liver effects observed at 150 mg/kg bw/day (REACHa).

In a 28-day repeat dose oral toxicity study (OECD TG 407), Wistar rats (n = 5/sex/dose) were administered allyl (3-methylbutoxy)acetate at 0, 25, 50 or 100 mg/kg bw/day. No mortalities or any clinical signs of toxicity were observed. There were no statistically significant changes in body weight between the treated and control groups. No statistically significant changes in haematology and biochemistry parameters were observed. The NOAEL for allyl (3-methylbutoxy)acetate was 100 mg/kg bw/day (REACHb).

In a 28-day repeat dose oral toxicity study (OECD TG 407), SD rats (n = 5/sex/dose) were administered allyl cyclohexyoxyacetate in the diet at doses corresponding to: 11.5 and 10.7 mg/kg bw/day, 32.8 and 32.3 mg/kg bw/day or 108.6 and 96.0 mg/kg bw/day, for males and females respectively. No mortality occurred. No substance-related toxic effects were observed, including at necropsy. No adverse effects were observed in the reproductive organs and tissues, sperm parameters, oestrus cycle or thyroid hormones. Based on this study, the NOAEL was 108.6 (males) and 96 mg/kg bw/day (females) (REACHc).

Metabolites:

The toxicity of allyl esters is associated with hydrolysis to allyl alcohol and subsequent conversion to acrolein, in particular hepatotoxicity due to rapid hydrolysis of the compounds in the liver. Studies on allyl alcohol have showed liver effects at 25 mg/kg bw/day in rats (NICNASd).

Adverse effects associated with alkoxyacetic acid metabolites of longer chain glycol ethers involve haemolytic anaemia, which is species specific and does not occur in humans. Systemic toxicity effects (reproductive, immunotoxicity) are reported for the methoxy and ethoxy analogues but not for longer chain analogues (ECETOC, 2005; NICNASb). In a 13-week study in rats, no significant reproductive toxicity effects was observed for animals treated with 2-butoxyethanol. Concurrent studies in rats with 2-methoxy- and 2-ethoxyethanol caused testicular atrophy in males. For 2-butoxyethanol, the NOAEL for haematotoxicity was 129 mg/kg bw/day for male rats. A LOAEL of 82 mg/kg bw/day for female rats was determined based on slight anaemia at the lowest tested dose (NICNASc). Therefore, it is not expected that the methyl-substituted buthoxy acetates allyl (3-methylbutoxy)acetate and allyl (2-methylbutoxy)acetate will be highly toxic.

Repeat dose toxicity studies using phenoxyethanol indicated that phenoxyacetic acid is not a potent haemolytic agent (ECETOC, 2005).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

No in vivo data are available. The available in vitro data for allyl phenoxyacetate, allyl (3-methylbutoxy)acetate and allyl cyclohexyoxyacetate do not indicate mutagenic potential.

In vitro

The following results were reported for allyl phenoxyacetate (REACHa):

- negative in bacterial reverse mutation assays (OECD TG 471) in several strains of *Salmonella typhimurium* (TA1535, TA1537, TA98 and TA100) and in *Escherichia coli* WP2 uvrA at concentrations up to 5000 µg/plate, with or without metabolic activation;
- negative in a mammalian cell HPRT gene mutation assay (OECD TG 476) in Chinese hamster lung fibroblasts (V79), with or without metabolic activation; and

- negative in a mammalian cell micronucleus test (OECD TG 487) in cultured human peripheral lymphocytes up to a concentration of 1922 µg/mL, with or without metabolic activation.

The following results were reported for allyl (3-methylbutoxy)acetate (REACHb)

- negative in bacterial reverse mutation assays (OECD TG 471) in several strains of *Salmonella typhimurium* (TA1535, TA1537, TA98, TA100 and TA102) at concentrations up to 2 µL/plate, with or without metabolic activation; and
- no induction of chromosome aberrations (OECD TG 473) in human peripheral blood lymphocytes up to a concentration of 1 µL/mL, with or without metabolic activation.

The following results were reported for allyl cyclohexyoxyacetate (REACHc):

- negative in bacterial reverse mutation assays (OECD TG 471) in several strains of *Salmonella typhimurium* (TA1535, TA1537, TA98,TA100 and TA102) at concentrations up to 5000 µg/plate, with or without metabolic activation;
- negative in a mammalian cell HPRT gene mutation assay (OECD TG 476) in V79 fibroblasts, with or without metabolic activation; and
- negative in a mammalian cell micronucleus test (OECD TG 487) in cultured human lymphocytes up to a concentration of 1983 µg/mL, with or without metabolic activation.

Metabolites

Available in vitro and in vivo data for allyl alcohol did not indicate mutagenic potential (NICNASd).

Data for 2-methoxy-, 2-ethoxy- and 2-butoxyethanol do not indicate significant genotoxic potential (ECETOC, 2005; NICNASb,c).

Carcinogenicity

No data are available.

The metabolites allyl alcohol and acrolein did not cause increased incidences of neoplastic changes compared with controls in oral gavage studies in rats and mice (NICNASa)

Reproductive and Developmental Toxicity

Limited data are available for the chemicals in this group. Based on the available information for allyl phenoxyacetate and the metabolites phenoxyacetic acid, allyl alcohol, acrolein and long-chain ethoxy alkyl groups, the chemicals in this group are not likely to be reproductive or developmental toxicants.

In a combined repeated dose/reproduction and developmental toxicity screening test, rats were administered allyl phenoxyacetate up to a dose of 150 mg/kg bw/day (see **Repeat dose toxicity: Oral** section). An increase in testes and epididymides weight was observed at 150 mg/kg bw/day. No adverse effects on fertility were observed in the parental animals (P0). In the first generation (F1) pups, decreased body weight was observed on postnatal day (PND) 13 at 150 mg/kg bw/day, likely to be secondary to parental toxicity. The developmental NOAEL was considered to be 50 mg/kg bw/day (REACHa).

Metabolites:

The metabolite phenoxyacetic acid was administered (gavage) to mice on gestation days (GD) 8–15 at a dose of 800–900 mg/kg bw, or on 3 consecutive days (GD 7–9, 10–12 or 13–15) at a dose of 250–300 mg/kg bw per day. The treated animals were euthanised on GD 18, and their uteri were examined. Foetuses were examined for gross external malformations, visceral abnormalities and skeletal malformations. The authors stated that phenoxyacetic acid was ‘not strongly teratogenic or foetotoxic’. No other details are available (JECFA, 2003).

Animal studies available for allyl alcohol and acrolein do not indicate significant toxicity to reproduction or development (NICNASa, d)

Reproductive toxicity in rats was observed for with 2-methoxy- and 2-ethoxyethanol, but not with 2-butoxyethanol (NICNASc).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation for the chemicals in this group include:

- systemic acute effects (acute toxicity from oral exposure).

Allyl (3-methylbutoxy)acetate (CAS No. 67634-00-8) may cause systemic acute effects (acute toxicity from inhalation exposure).

Allyl phenoxyacetate (CAS No. 7493-74-5) may cause local effects (skin sensitisation).

Public Risk Characterisation

While uses of the chemicals in Australia were not identified, the chemicals are reported to be used in cosmetics and domestic products, particularly perfumery, overseas. The general public could be exposed through the skin when using cosmetic and domestic products containing the chemicals. At present, specific allyl esters fall within the scope of the listing of ‘ALLYL ESTERS' in Schedule 6 of the SUSMP, while unspecified esters are in Schedule 7 as derivatives of allyl alcohol.

At present, as derivatives, the chemicals fall within the scope of the listing of ‘allyl alcohol' in Schedule 7 of the SUSMP. It is recommended that these allyl esters are exempted from the Schedule 7 entry, considering the acute toxicity values are consistent with inclusion in a lower schedule and dermal exposure to the chemicals will be at low concentrations. A concentration cut-off for free allyl alcohol consistent with IFRA controls and the current entry in the Poison Standard for allyl esters is recommended.

Occupational Risk Characterisation

During product formulation, 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. 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 chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals 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) (refer to **Recommendation** section).

NICNAS Recommendation

Changes to risk management are required. Sufficient information is available to recommend that risks to public health and safety from the potential uses of these chemicals in cosmetics and domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

The following amendments to the SUSMP are recommended:

- inclusion of this group of chemicals into Schedule 6 'ALLYL ESTERS'.

While these allyl esters are not expected to be used at concentrations >5 %, it is recommended that they be aligned with the other allyl esters by inclusion to the Schedule 6 entry for allyl esters.

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

Note: The acute toxicity (inhalation) classification applies to allyl (3-methylbutoxy)acetate only (CAS No. 67634-00-8). The sensitisation classification will only apply to allyl phenoxyacetate (CAS No. 7493-74-5).

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 if inhaled - Cat. 4 (H332)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (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 oral, dermal and inhalation 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.

References

ChemID Plus Advanced. Accessed April 2019 at **https://chem.nlm.nih.gov/chemidplus/**

Cosmetic Ingredients& Substances (CosIng) Database. European Commission. Accessed April 2019 at **http://ec.europa.eu/consumers/cosmetics/cosing/**

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2005. Technical Report No 95. The Toxicology of Glycol Ethers and its Relevance to Man (Fourth Edition) Volume 1. Accessed April 2019 at **http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-095-Vol-I.pdf**

Galleria Chemica. Accessed April 2019 at **http://jr.chemwatch.net/galleria/**

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

International Fragrance Association (IFRA) Transparency List. Accessed June 2019 at **https://ifrafragrance.org/initiatives/transparency/ifra-transparency-list**

Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2003. WHO Food Additives Series 50: Phenthyl alcohol, aldehyde, acid and related acetals and esters. Accessed April 2019 at **http://www.inchem.org/documents/jecfa/jecmono/v50je11.htm**

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for Aliphatic allyl esters. Available at **http://www.nicnas.gov.au**

National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for Alkoxyethanols (C1-C2) and their acetates. Available at **http://www.nicnas.gov.au**

National Industrial Chemicals Notification and Assessment Scheme (NICNASc). Priority Existing Chemical assessment (PEC) for 2-butoxyethanol. Available at **http://www.nicnas.gov.au**

National Industrial Chemicals Notification and Assessment Scheme (NICNASd). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for Allyl alcohol. Available at **http://www.nicnas.gov.au**

Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed April 2019 at **http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp**

Personal Care Products Council 2011. Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 1st Edition.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHa). Allyl phenoxyacetate (CAS No. 7493-74-5). Accessed April 2019 at **https://echa.europa.eu/web/guest/information-on-chemicals/registeredsubstances**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHb). Allyl (3-methylbutoxy)acetate (CAS No. 67634-00-8). Accessed April 2019 at **https://echa.europa.eu/web/guest/information-on-chemicals/registeredsubstances**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHc). Allyl (cyclohexyloxy)acetate (CAS No. 68901-15-5). Accessed April 2019 at **https://echa.europa.eu/web/guest/information-on-chemicals/registeredsubstances**

Safe Work Australia (SWA). Hazardous Chemical Information System (HCIS). Accessed April 2019 at **http://hcis.safeworkaustralia.gov.au/**

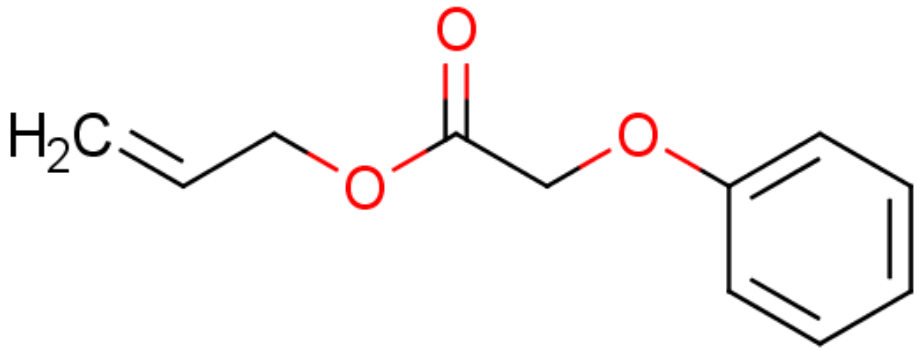
The Poisons Standard June 2019. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 24. Accessed June 2019 at **https://www.tga.gov.au/publication/poisons-standard-susmp**

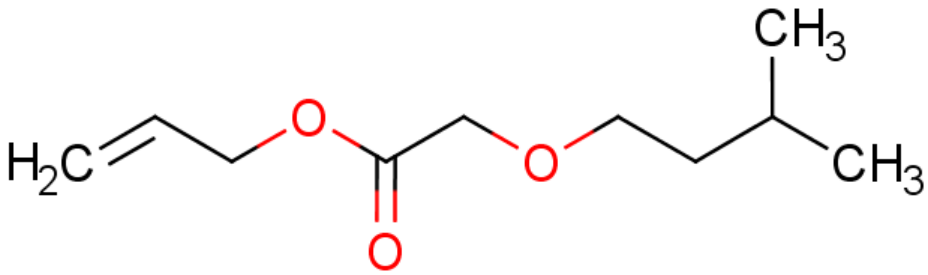
United States (US) National Library of Medicine's Household Products Database, Health and Safety Information on Household Products. Accessed April 2019 at **http://householdproducts.nlm.nih.gov/**

Last Update 28 June 2019

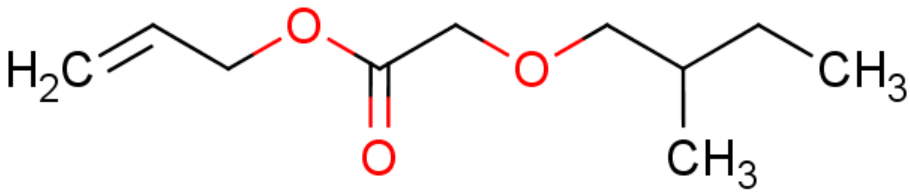
Chemical Identities

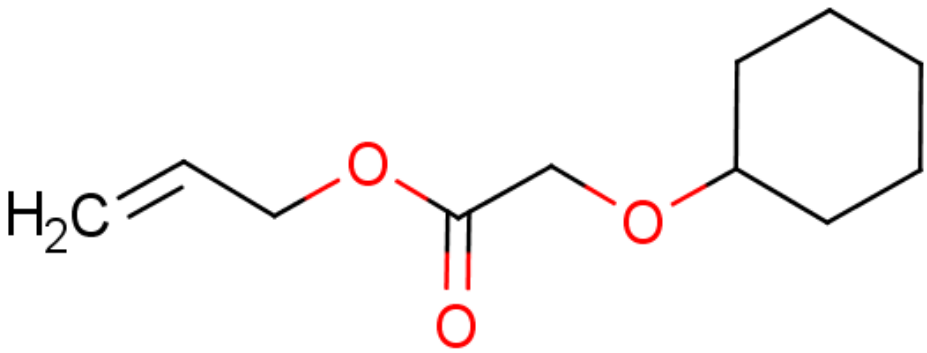
Chemical Name in the Inventory and Synonyms	**Acetic acid, phenoxy-, 2-propenyl ester** acetic acid, phenoxy, allyl ester allyl phenoxyacetate 2-propenyl phenoxyacetate
CAS Number	7493-74-5
Structural Formula	

	
Molecular Formula	C11H12O3
Molecular Weight	192.21

Chemical Name in the Inventory and Synonyms	**Acetic acid, (3-methylbutoxy)-, 2-propenyl ester** isoamyloxyacetic acid, allyl ester allyl (3-methylbutoxy)acetate
CAS Number	67634-00-8
Structural Formula	
Molecular Formula	C10H18O3
Molecular Weight	186.25

Chemical Name in the Inventory and Synonyms	**Acetic acid, 2-(2-methylbutoxy)-, 2-propenyl ester** allyl (2-methylbutoxy)acetate
CAS Number	67634-01-9
Structural Formula	

	
Molecular Formula	C10H18O3
Molecular Weight	186.25

Chemical Name in the Inventory and Synonyms	**Acetic acid, (cyclohexyloxy)-, 2-propenyl ester** allyl cyclohexyloxyacetate
CAS Number	68901-15-5
Structural Formula	
Molecular Formula	C11H18O3
Molecular Weight	198.26

Share this page