

Aliphatic allyl esters: Human health tier II assessment

02 March 2018

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Chemicals in this assessment

| Chemical Name in the Inventory | CAS Number |
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| Butanoic acid, 2-propenyl ester | 2051-78-7 |
| Hexanoic acid, 2-propenyl ester | 123-68-2 |
| Heptanoic acid, 2-propenyl ester | 142-19-8 |
| Acetic acid, 2-propenyl ester | 591-87-7 |
| Benzeneacetic acid, 2-propenyl ester | 1797-74-6 |
| Propanoic acid, 2-propenyl ester | 2408-20-0 |
| Cyclohexanepropanoic acid, 2-propenyl ester | 2705-87-5 |
| Butanoic acid, 3-methyl-, 2-propenyl ester | 2835-39-4 |
| Octanoic acid, 2-propenyl ester | 4230-97-1 |
| Cyclohexaneacetic acid, 2-propenyl ester | 4728-82-9 |
| Pentanoic acid, 2-propenyl ester | 6321-45-5 |

| Chemical Name in the Inventory | CAS Number |
|--|------------|
| Nonanoic acid, 2-propenyl ester | 7493-72-3 |
| Decanoic acid, 2-propenyl ester | 57856-81-2 |
| Hexanoic acid, trimethyl-, 2-propenyl ester | 68132-80-9 |

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

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are esters of allyl alcohol (CAS No. 107-18-6). Given the close structural similarities of the chemicals in this group and common esterase activity producing a toxic metabolite, they are expected to have essentially similar toxicokinetics. Most of the chemicals in this group have similar uses, they are used in food flavouring or as a fragrance component.

Following administration by oral and inhalation routes, the chemicals in this group are readily absorbed and rapidly converted to the parent alcohol (allyl alcohol) and the corresponding acids, by hydrolysis of the ester linkage, either under acidic conditions in the stomach or by esterases throughout the body (see **Toxicokinetics** section). The data available indicate that the effects on human health are expected to be driven by the metabolite (see **Health Hazards** section).

Limited data is available for the chemicals. Therefore, where toxicological data are lacking for specific endpoints in this assessment in identifying hazards associated with these chemicals, data available for other structurally related allyl esters, and the metabolites are considered relevant for 'read-across', particularly for long-term toxicity. The metabolites of allyl alcohol, acrylic acid (CAS No. 79-10-7) and glycidol (CAS No. 556-52-5), have both been previously assessed by NICNAS and have been taken into account in this assessment, where relevant (NICNASa; NICNASb). The metabolite of allyl acetate (acetic acid (CAS No. 64-19-7)), has been previously assessed by NICNAS and has been taken into account in this assessment, where relevant (NICNASc).

Whilst there may be differences between the allyl acetate and the other allyl esters within this group with respect to local effects, allyl alcohol is considered the main moiety responsible for the toxicity; hence, they are considered here together. The carboxylate ions produced by ester hydrolysis *in vivo* are all expected to have low toxicity.

Import, Manufacture and Use

Australian

Allyl hexanoate (CAS No. 123-68-2) has reported domestic uses in automobile cleaning and polishing products, and reported commercial use as an industrial rubbing compound.

Allyl cyclohexanepropionate (CAS No. 2705-87-5) has reported domestic and commercial uses in automobile cleaning and coating products.

No specific Australian use, import, or manufacturing information has been identified for other chemicals in this group.

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 Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US Household Products Database; and the International Fragrance Association (IFRA) Transparency List.

All chemicals in this group, except for allyl acetate (CAS No. 591-87-7) and allyl pentanoate (CAS No. 6321-45-5), have reported cosmetic use in perfumes or as fragrance ingredients. Allyl isovalerate (CAS No. 2835-39-4) has reported cosmetic and domestic use as a fragrance, in perfumes (0.05–0.08 %), creams and lotions (0.0015–0.0070 %), soap (0.003–0.2 %) and in detergent (0.0003 %) (CalEPA, 2002).

Allyl hexanoate (CAS No. 123-68-2) has additional reported uses in cosmetics as an astringent, emollient and masking agent (CosIng).

Allyl butyrate (CAS No. 2051-78-7) is listed on CosIng as a fragrance ingredient. However, IFRA has delisted the chemical from the transparency list and categorised it as 'fragrance materials not supported for use due to insufficient data (IFRA, 2017). Allyl isovalerate has also been delisted from the IFRA transparency list (IFRA, 2017).

There is currently no documented use of the chemicals in the Compilation of Ingredients used in Cosmetics in the United States (CIUCUS, 2011).

Allyl hexanoate and allyl heptanoate (CAS No. 142-19-8) and allyl cyclohexanepropionate (CAS No. 2705-87-5) have reported domestic uses in air fresheners (up to 5 % for allyl hexanoate), surface wipes, scented oils and wax (Household Products Database). Allyl nonanoate (CAS No. 7493-72-3) has reported domestic use as a surfactant (NTP).

Allyl cyclohexanepropionate (CAS No. 2705-87-5) has commercial uses in polishes, wax blends, washing and cleaning products.

Allyl acetate (CAS No. 591-87-7) has reported site-limited use to produce allyl alcohol. Allyl cyclohexanepropionate has reported site-limited use as an intermediate.

The chemicals have reported non-industrial use as food additives. Allyl hexanoate has reported non-industrial use as an additive in cigarettes. Allyl cyclohexanepropionate has reported non-industrial use as a biocide.

Restrictions

Australian

The chemicals in this group are not specifically restricted.

However, the metabolites of allyl esters, acrolein and allyl alcohol are listed in the *Poisons Standard—The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 7 (SUSMP, 2017).

Schedule 7 chemicals are described as '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'. Schedule 7 chemicals are labelled with 'Dangerous Poison' (SUSMP, 2017).

The Schedule 7 entry for allyl alcohol includes derivatives, such as esters; therefore, the chemicals in this group are included in Schedule 7.

International

The chemicals are listed on 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 %);
- 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, 2017).

Others:

The chemicals have no safety concern at current levels of intake when used as a flavouring agent. Acceptable daily intake up to 0.13 mg/kg bw daily for allyl hexanoate, up to 0.15 mg/kg bw daily for allyl heptanoate, and up to 0.12 mg/kg bw daily for allyl isovalerate (equivalent to 0.05 mg/kg bw allyl alcohol, for allyl hexanoate, allyl heptanoate and allyl isovalerate) (JECFA, 1991).

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 hydrolysed in the body to form the parent alcohol (allyl alcohol) and corresponding acids. The data available (see **Health Hazards** section) indicate that the effects on human health are expected to be driven by the metabolite, allyl alcohol. Therefore, where available, data from the parent alcohol, the corresponding acids and the metabolites are considered as suitable analogues for systemic effects, particularly for long-term toxicity.

Toxicokinetics

Several studies on the metabolism of allyl esters in animals are available. Through the available metabolism and excretion data and read-across from structurally similar chemicals, the chemicals are expected to be rapidly and almost completely absorbed and metabolised and predominantly excreted in the urine.

In vivo, these chemicals are hydrolysed enzymatically to allyl alcohol and the corresponding acids. Whilst the acid moiety may play a role in the local effects, the systemic toxicity of these chemicals is a result of the metabolites. For example, allyl isovalerate (CAS No. 2835-39-4) is metabolised to allyl alcohol and isovaleric acid (CAS No. 503-74-2). Isovaleric acid is then converted to isovaleryl-coenzyme A (CoA), a naturally occurring compound in humans, rats and mice. In humans with metabolic defects, the presence of high levels of isovaleric acid in blood causes toxicity effects such as vomiting and lethargy, further developing to pancytopenia, coma and ketoacidosis (NTP, 1983). Allyl alcohol is then distributed in the liver and further oxidised by hepatic alcohol dehydrogenase (ADH) to the highly reactive aldehyde acrolein, which is subsequently oxidised by aldehyde dehydrogenase (ALDH) to acrylic acid. Both allyl alcohol and acrolein can also undergo hepatic microsomal oxidation to form glycidol and glycidaldehyde, respectively. The glycidol may then be converted to glycerol by epoxide hydrolase. However, the amount of glycidol formed following metabolism of the esters is unknown (NTP, 1983; JECFA, 1991; CalEPA, 2002; OECD, 2016).

Acrolein can also react readily with hepatic glutathione (GSH) to form adducts, leading to GSH depletion and oxidative stress. This conjugate is excreted in urine as 3-hydroxypropylmercapturic acid (3-HPM). Acrolein can also react nonenzymatically with cellular macromolecules (via Michael additions), contributing to cytotoxic effects. Overall, the reactivity of acrolein is associated with the hepatotoxicity and cellular damage observed with the chemical (NTP, 1983; JECFA, 1991; CalEPA, 2002; OECD, 2016).

Allyl isovalerate (as a branched chain ester), showed a slower hydrolysis rate in vitro compared with straight chain allyl esters (JECFA, 1991). In vitro data indicate that chemicals are rapidly enzymatically metabolised. In an in vitro hydrolysis study, allyl

hexanoate (CAS No. 123-69-2) hydrolysed slowly in artificial gastric juice (half life (t_{1/2}) = 1120 minutes) but more rapidly in artificial pancreatic juice (t_{1/2} = 1.98 minutes). Allyl hexanoate hydrolysed very rapidly in in vitro preparations of rat liver homogenates (t_{1/2} = 3.96 seconds) and rat small intestinal mucosa (t_{1/2} = 0.096 seconds) (REACHa). Similar hydrolytic data were reported for the structural analogues of allyl heptanoate, allyl octanoate, and allyl nonanoate in rat pancreatic preparations. Increasing the straight-chain length did not markedly decrease the rate of enzymatic hydrolysis compared to hexanoate (OECD, 2016).

Linear saturated aliphatic carboxylic acid esters metabolise to coenzyme A thioesters and then enter the fatty acid β-oxidation pathway. The acids may oxidise to diacids with increasing carbon chain length (REACHb). Saturated aliphatic carboxylic acid metabolites are generally considered to not cause severe hepatotoxic effects due to being less reactive (OECD, 2016).

Allyl acetate is reported to be absorbed through intact skin (NTP, 1993). The increased carbon numbers of the alkyl chain may contribute to increased hydrophobicity (OECD, 2016).

Acute Toxicity

Oral

Based on the available data, the chemicals are considered to be acutely toxic and hazard classification is warranted (see **Recommendation** section).

The reported median lethal doses (LD₅₀) values are:

- allyl acetate (CAS No. 591-87-7), 130–142 mg/kg bw in rats and 170 mg/kg bw in mice (Galleria Chemica; HSDB);
- allyl butyrate (CAS No. 2051-78-7), 250 mg/kg bw in rats (Galleria Chemica);
- allyl hexanoate (CAS No. 123-68-2), 218–393 mg/kg bw in rats and 280 mg/kg bw in guinea pigs (JECFA, 1991);
- allyl heptanoate (CAS No. 142-19-8), 500 mg/kg bw in rats, 630 mg/kg bw in mice, and 444 mg/kg bw in guinea pigs (JECFA, 1991);
- allyl isovalerate (CAS No. 2835-39-4), 230 mg/kg bw in rats and ≥500 mg/kg bw in mice. Decreased activity, ruffled fur and yellowed faeces were observed in all animals that received 500 mg/kg bw (Galleria Chemica; NTP, 1983). No other effects were reported.
- allyl phenylacetate (CAS No. 1797-74-6), 650 mg/kg bw in rats (Galleria Chemica);
- allyl cyclohexanepropionate (CAS No. 2705-87-5), 585 mg/kg bw in rats and 380 mg/kg bw in guinea pigs. Depression and rough fur in rats, and salivation and haemorrhage in the small intestine in guinea pigs were reported (REACH)
- allyl cyclohexaneacetate (CAS No. 4728-82-9), 900 mg/kg bw in rats; and
- allyl trimethylhexanoate (CAS No. 68132-80-9), 1400 mg/kg bw in rats.

Allyl esters are expected to be hydrolysed in the acidic conditions of the stomach to allyl alcohol and the corresponding carboxylic acid, which are further metabolised within the body. The metabolites (except acetic acid, isovaleric acid and pentanoic acid) are also acutely toxic by oral route. The available oral LD₅₀ of the metabolites in rats are:

- allyl alcohol (CAS No. 107-18-6), 64 mg/kg bw (REACHc);
- acrolein (CAS No. 107-02-8), 10.3 mg/kg bw and 11.8 mg/kg bw for males and females, respectively (CLH, 2011);
- acrylic acid (CAS No. 79-10-7), 1350 mg/kg bw (NICNASa);
- glycidol (CAS No. 556-52-5), 420–850 mg/kg bw (NICNASb);
- acetic acid (CAS No. 64-19-7), >2000 mg/kg bw (NICNASc);

- isovaleric acid (CAS No. 503-74-2), >2000 mg/kg bw (REACHe);
- butyric acid (CAS No. 107-92-6), 2000 mg/kg bw (NICNASd);
- propanoic acid (CAS No. 79-09-4), 351–4290 mg/kg bw (NICNASE); and
- pentanoic acid (CAS No. 109-52-4), 4600 mg/kg bw (Galleria Chemica).

On the basis of allyl alcohol content, the LD50 values in rats above are:

- allyl acetate, 75–82 mg/kg bw;
- allyl butyrate, 113 mg/kg bw;
- allyl hexanoate, 90–146 mg/kg bw;
- allyl heptanoate, 170 mg/kg bw;
- allyl isovalerate, 94 mg/kg bw.
- allyl phenylacetate, 221 mg/kg bw;
- allyl cyclohexanepropionate, 173 mg/kg bw;
- allyl cyclohexaneacetate, 286 mg/kg bw; and
- allyl trimethylhexanoate, 409 mg/kg bw.

Dermal

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

The reported dermal LD50 values in rabbits are (Galleria Chemica; IARC, 1985; JECFA, 1991):

- allyl acetate (CAS No. 591-87-7), 1021 mg/kg bw;
- allyl butyrate (CAS No. 2051-78-7), 530 mg/kg bw;
- allyl hexanoate (CAS No. 123-68-2), 300 mg/kg bw;
- allyl heptanoate (CAS No. 142-19-8), 810 mg/kg bw;
- allyl isovalerate (CAS No. 2835-39-4), 560 mg/kg bw;
- allyl cyclohexanepropionate (CAS No. 2705-87-5), 1600 mg/kg bw (REACH); and
- allyl cyclohexaneacetate (CAS No. 4728-82-9), 1250 mg/kg bw.

Allyl esters are expected to be absorbed to some extent through intact skin due to their lipophilicity and small molecular weight. Esterases present in the dermis of the skin can metabolise the chemical, which may alter the systemic bioavailability of the chemical by the dermal route. However, the metabolites are also acutely toxic by dermal route. The available dermal LD50 of the metabolites in rabbits are:

- allyl alcohol (CAS No. 107-18-6), 89 mg/kg bw (REACHc);
- acrolein (CAS No. 107-02-8), 231 mg/kg bw (CLH, 2011);
- acrylic acid (CAS No. 79-10-7), 640 mg/kg bw (NICNASa);

- glycidol (CAS No. 556-52-5), 1980 mg/kg bw (NICNASb);
- acetic acid (CAS No. 64-19-7), 1060 mg/kg bw (NICNASc);
- isovaleric acid (CAS No. 503-74-2), >2000 mg/kg bw (REACHe);
- butyric acid (CAS No. 107-92-6), 6077 mg/kg bw (NICNASd);
- propanoic acid (CAS No. 79-09-4), 490 mg/kg bw (NICNASe); and
- pentanoic acid (CAS No. 109-52-4), 530 mg/kg bw (Galleria Chemica).

Inhalation

Based on the data available for allyl acetate and other metabolites, the chemicals are considered to have low to moderate acute toxicity following inhalation exposure.

The reported median lethal concentration (LC50) for allyl acetate in rats is 1000 ppm (~1.02 mg/L) after a one hour exposure. No other details are available (Galleria Chemica).

The available LC50 values for the metabolites are:

- acetic acid (CAS No. 64-19-7), 11.4 mg/L for a four hours in rats (NICNASc);
- butyric acid (CAS No. 107-92-6), >500 mg/m³ (0.5 mg/L) in rats and mice (NICNASd);
- propanoic acid (CAS No. 79-09-4), >19.7 mg/L in rats (NICNASe);
- pentanoic acid (CAS No. 109-52-4), 4100 mg/m³ (4.1 mg/L), two hours in mice (Galleria Chemica).

Corrosion / Irritation

Corrosivity

Based on the available data and physicochemical properties, there is sufficient evidence to classify allyl acetate as corrosive. This classification does not apply to the other chemicals in the group.

Allyl acetate is reported to cause severe skin and eye burns leading to permanent damage (NJDoHSS, 1989; also see **Observation in Humans** section).

Respiratory Irritation

When heated to decomposition, allyl acetate produces acrid smoke and the fumes are irritating to the respiratory system, causing coughing or shortness of breath. Higher exposures are reported to cause pulmonary oedema (NJDoHSS, 1989; NTP, 2006). Acetic acid is also reported to cause extreme nasal irritation (NICNASc).

Skin Irritation

Allyl isovalerate, allyl hexanoate and allyl heptanoate, allyl butyrate, allyl phenylacetate and allyl cyclohexaneacetate have been reported as slightly to moderately irritating to the skin (JECFA, 1991; REACHa; REACHb). However, data available are not sufficient for hazard classification.

During an acute dermal toxicity study on allyl heptanoate in rabbits, skin irritancy was evaluated on day 1. At dermal doses of 313–1250 mg/kg slight to moderate redness and oedema were reported (JECFA, 1991).

In a skin irritation study (based on EEC Commission Directive 1984) in New Zealand White (NZW) rabbits (6 groups of 4), 0.5 mL of allyl heptanoate was applied (semi-occluded) to the flanks of the animals for 4 hours, with observation up to 7 days. Slight to well-defined erythema (score = 1.5) was observed in 1 animal at 1 hour after treatment, and the rest displayed very slight erythema (score = 1.0). At the 24-hour timepoint, well-defined erythema was observed in 3 animals (score = 2.0) and remained in 2 animals up to the 72-hour timepoint. Oedema (score = 0.5) was observed in all animals up to 72 hours but was fully reversible after 7 days. The average scores at 24, 48 and 72 hours were 1.7 for erythema and 0.4 for oedema (REACHb).

An in vitro study using the reconstructed human epidermis (RhE) (OECD Guideline Draft Proposal for in vitro skin irritation) was performed on allyl hexanoate and allyl heptanoate. The chemicals were applied undiluted at 15 µL to 3 tissues for 15 minutes at 37 °C, then incubated for 42 hours at 37 °C. At the 15-minute treatment interval, only slight skin irritation was observed (REACHa; REACHb).

Allyl isovalerate, allyl butyrate, allyl phenylacetate and allyl cyclohexaneacetate were reported to be moderately irritating when applied undiluted to intact or abraded rabbit skin under occlusion for 24 hours (Opdyke, 1974; JECFA, 1991).

The skin irritation potential of allyl cyclohexanepropionate was assessed using the Human Skin Model Test (OECD TG 439). The human skin model EpiSkin™ was treated with 10 µL of the chemical, the negative or positive control for 15 minutes, followed by 42 hours incubation. The mean relative absorbance (% of negative control) for the chemical decreased to 93.9 %, which is well above the threshold for irritancy of ≤50 %. Under the conditions of this study, the chemical is not considered to be a potential skin irritant (REACHg).

The Quantitative Structure Activity Relationship (QSAR) modelling for the allyl esters using the Optimised Approach based on Structural Indices Set-Tissue MEtabolism Simulator (OASIS-TIMES, version 2.27.19) program gave positive predictions for skin irritation of the carboxylic acid esters. The results were within the applicability domain.

Eye Irritation

Data are available for allyl hexanoate and allyl cyclohexanepropionate, which are slight eye irritants. However, the incidence and severity of these effects are not sufficient to warrant hazard classification. No information is available for the shorter chain esters.

In an eye irritation test (OECD test guideline 405), allyl hexanoate (0.1 mL) was instilled in the left eye of 4 SPF albino rabbits. At 1 hour after application of the test substance, all animals showed weak conjunctival effects. No sign of eye irritation was observed after 24, 48 and 72 hours in any of the animals. The reported scores were cornea opacity = 0.0; iris lesion = 0.0; redness of conjunctiva = 0.3; and oedema of conjunctiva (chemosis) = 0.0 (REACHa; REACHb).

In an eye irritation test (OECD test guideline 405), allyl cyclohexanepropionate (0.1 mL) was instilled into SPF albino rabbits (Mol: Russian). Slight conjunctival effects were observed at 1, 24 and 48 hours following treatment in all animals. At 72 hours, 1 animal showed injected conjunctival vessels and abnormal swelling, while the others did not show exhibit any effects. The reported mean scores for 24, 48 and 72 hours were cornea opacity = 0.0; iris lesion = 0.0; conjunctivae = 0.8; and chemosis = 0.8. All effects were fully reversibly and no reactions were observed in all animals after seven days. The chemical was concluded to be non-irritating (REACHg).

The QSAR modelling for allyl esters using the Optimised Approach based on Structural Indices Set-Tissue MEtabolism Simulator (OASIS-TIMES, version 2.27.19) program gave positive predictions for eye irritation as esters. However, the results were outside the applicability domain.

Other

Although no data on eye irritation is available for allyl isovalerate, the chemical was reported to be an irritant to mucosal surfaces of the stomach or forestomach in both rats and mice. Rats administered the chemical at 500 mg/kg bw for 2 days had dark red areas on the stomach wall (3/5 males and 3/5 females) (NTP, 1983). In longer term studies, thickening of the intestinal wall and reddening of the mucosal surfaces in the intestines and urinary bladder was observed. No lesions were detected histopathologically (see **Repeat Dose Toxicity** section).

Observation in humans

The vapour of allyl acetate is stated to be irritating to the skin and mucous membranes, causing lacrimation and corneal burns. Undiluted liquid allyl acetate can cause first to second-degree burns when in contact with skin (NTP, 2006). Prolonged contact is stated to cause a 'rash with itching and redness' (NJDoHSS, 1989).

In a 48-hour patch test, allyl hexanoate was applied on the forearms of human volunteers (n = 5). Four subjects displayed grade 1 irritation. However in a subsequent study by the same author using both allyl hexanoate and heptanoate, no signs of irritation were observed in 5 volunteers (JECFA, 1991).

Allyl isovalerate was not irritating when applied to the backs of 28 subjects in a closed patch test (JECFA, 1991).

Allyl butyrate and allyl cyclohexaneacetate produced slight irritation at a concentration of 4 % in petrolatum in a 48-hour closed-patch test on human subjects (Opdyke, 1979).

Allyl cyclohexanepropionate was not an irritant in a patch test on 129 human volunteers at concentrations up to 2 %. The chemical (0.3 mL) was applied (occlusively) to the back for 24 hours and responses were assessed up to 5 days following exposure. The chemical caused less irritation compared with the other allyl esters tested (allyl hexanoate, allyl cyclohexyloxyacetate, allyl phenoxyacetate) (REACHg). In another 24-hour patch test, allyl cyclohexanepropionate (20 µg) was positive in 8 out of 10 volunteers, and allyl heptanoate was positive in 9 out of 10 volunteers. The concentrations were not reported. Although these chemicals were reported to be acute irritants, the data were not considered to be relevant for classification (REACHg)

Allyl phenylacetate showed mixed results in two 48-hour closed patch tests on human subjects, when tested up to 12 % in petrolatum. No irritation reactions were reported initially, but were observed when retested. When tested at 6 %, it was a significant irritant in a majority of human subjects (Opdyke, 1979).

Sensitisation

Skin Sensitisation

Based on the limited animal and human (see **Observation in Humans** section) data, the chemicals are not expected to have skin sensitisation potential. However allyl cyclohexanepropionate is a moderate skin sensitizer in guinea pigs.

In a guinea pig maximisation test study (OECD TG 406), male Dunkin-Hartley guinea pigs (n = 20) were intradermally induced with 5 % allyl heptanoate in sesame oil. This was followed by topical exposure to 50 % allyl heptanoate in sesame oil for 48 hours, 1 week after the injections. After a 14-day non-treatment period, the animals were challenged with occlusive patches of 1 % allyl heptanoate in sesame oil for a 24-hour period. Observations were made at 24 and 48 hours. Discrete or patchy erythema was observed in both treated as well as controls animals, indicating the irritating effect of the chemical (REACHb).

In another guinea pig maximisation test study (OECD TG 406), male and female Hartley guinea pigs (n = 20) were intradermally induced with 5 % allyl cyclohexanepropionate in paraffin oil, followed by topical induction to 100 % of the chemical. The challenge concentrations were the same as for induction. Animals (n = 13) showed a positive response to the substance at 24 and 48 hours, indicating a moderate sensitizer. Under the conditions of this study, the chemical is a sensitizer (REACHg).

Limited human data have shown that the chemicals are not skin sensitizers in human volunteers (see **Observation in Humans** section).

Testing on the metabolites allyl alcohol, acrolein and acrylic acid did not show skin sensitisation potential in guinea pigs and humans (CLH, 2011; NICNASa; REACHa; REACHb).

Propanoic acid was not sensitising in guinea pigs (NICNASE). Other aliphatic carboxylates are not expected to be skin sensitizers.

Using the OECD Toolbox (version 3.4), QSAR modelling gave a structural alert for protein binding, based on activated alkyl esters and thioesters. The suggested mechanism for protein reactivity is nucleophilic substitution on an activated carbon atom,

which in this case, is the allyl moiety of the compound. Using OASIS-TIMES (version 2.27.19), QSAR modelling resulted in a prediction of a weak sensitiser for the parent, and non-sensitising for the metabolite. However, the prediction was out of the applicability domain.

Observation in humans

In a maximisation test with allyl hexanoate, positive reactions in 13 out of 25 volunteers were reported; this was in contrast with an earlier maximisation test on a similar number of volunteers in which no sensitisation was detected (JECFA, 1991). No sensitisation was reported for allyl heptanoate using a similar protocol (JECFA, 1991).

Allyl isovalerate was not a skin sensitiser in a maximisation test in 28 volunteers (JECFA, 1991). Another maximisation test in volunteers gave negative results following application of the chemical at 1 % (IARC, 1985).

Positive results were reported for allyl phenylacetate at 12 % in a human maximisation test in 25 volunteers. Testing had to be stopped on the third induction day due to the severity of the reactions. This chemical was considered to have an unusually high content of free allyl alcohol (present at 0.3 %) and no similar reactions with other allyl compounds were observed. After removal of allyl alcohol content and retesting at a concentration of 3 % in 33 volunteers, irritation was still present but no reactions for sensitisation were observed (Opdyke, 1979; RIFM, 2015)

Allyl butyrate, allyl cyclohexaneacetate and allyl cyclohexanepropionate were not skin sensitisers when tested at a concentration of 4 % in maximisation tests on 23–28 volunteers (Opdyke, 1979).

Repeated Dose Toxicity

Oral

The effects observed in the repeated dose studies suggest that the liver, stomach and hematopoietic system in rats and mice are the primary sites affected following treatment with allyl esters. The mechanism of hepatotoxicity of allyl esters is linked to its rapid hydrolysis in the liver to the metabolites; allyl alcohol and acrolein (see **Toxicokinetics** section). Many studies on allyl alcohol and acrolein have showed liver damage, often localised to the periportal region. Based on the treatment-related effects reported in various repeated dose toxicity studies, allyl acetate is considered to cause serious damage to health from repeated oral exposure, and classification is warranted. This classification does not apply to the other chemicals in the group.

Among the available data, allyl acetate displayed the most severe effects in rats and mice, with mice less sensitive than rats. Forestomach lesions were observed with allyl acetate at ≥ 12 mg/kg bw/day and with allyl isovalerate at 250 mg/kg bw/day, but not with allyl hexanoate and heptanoate. For allyl acetate, hepatotoxicity was observed at ≥ 25 mg/kg bw/day and this is more relevant for systemic toxicity as forestomach irritation is an anticipated effect of gavage studies (OECD, 2016). Hepatotoxicity was the least severe with allyl heptanoate and observed at 100 mg/kg bw/day. Therefore, repeat dose effects may be less severe with increasing carbon chain lengths for linear alkyl chains, consistent with toxicity due to the allyl alcohol component.

In a 14-week oral gavage study conducted by the National Toxicology Program (NTP), F344/N rats were administered allyl acetate at 0, 6, 12, 25, 50 or 100 mg/kg bw/day, and B6C3F1 mice were administered 0, 8, 16, 32, 62.5 or 125 mg/kg bw/day. At the highest doses, all animals either died or were moribund by the first week. Rats at the highest dose developed forestomach necrosis, haemorrhage and inflammation. Significantly increased incidences of glandular stomach haemorrhage were observed in male mice at 62.5 mg/kg bw/day. Forestomach squamous epithelial hyperplasia was observed in rats at ≥ 12 mg/kg bw/day, and in mice at ≥ 16 mg/kg bw/day. Bone marrow hyperplasia, lymph node depletion and thymus necrosis were observed in rats at 100 mg/kg bw/day and in mice at 62.5 mg/kg bw/day. Increased incidences of liver lesions (periportal hepatocyte hypertrophy and mitotic alteration, mineralisation, haemosiderin pigmentation, portal fibrosis and granulomatous inflammation) were observed in rats at ≥ 25 mg/kg bw/day and in mice at ≥ 62.5 mg/kg bw/day (NTP, 2006). The no observed adverse effect level (NOAEL) was determined as 6 and 8 mg/kg bw/day in rats and mice, respectively.

In a 13-week dose-ranging study conducted by the National Toxicology Program (NTP), groups of B6C3F1 mice and F344/N rats ($n = 10/\text{sex}/\text{dose}$) were administered allyl isovalerate (via gavage) in corn oil at doses from 0, 15, 31, 62, 125 or 250 mg/kg bw/day, 5 days a week. Both the control and high-dose groups were examined histologically. At the highest dose, mortalities occurred in all males and 4 out of 10 females. Other effects observed at this dose included ulcerative inflammation of the

stomach, thickening of the stomach mucosa and thickening of the urinary bladder wall and liver lesions. In mice, mean body weight gains were depressed by 10 % in both sexes. In rats, mean body weight gains were depressed by 14 % in males at 125 mg/kg bw/day, and by 16 % in females at 250 mg/kg bw/day. At ≥ 125 mg/kg bw/day, thickening of the urinary bladder wall, stomach mucosa and small intestine were observed in both species. No compound-related histopathological effects were observed on the liver, stomach or bladder in other treated groups (NTP, 1983). The NOAEL was determined as 62 mg/kg bw/day. Liver effects observed at ≥ 125 mg/kg included multifocal coagulative necrosis, cholangiofibrosis, nodular hyperplasia and bile duct hyperplasia in both sexes of rats and mice. In male rats, cytoplasmic vacuolisation was observed at all doses. No NOAEL could be determined for male rats, but for female rats, 62 mg/kg bw/day was reported. A NOAEL of 62 mg/kg bw/day was reported for mice (NTP, 1983).

In 2 short-term (14 day) oral studies, rats and mice ($n = 5/\text{sex}/\text{dose}$) were administered allyl isovalerate (gavage) in corn oil at doses of 0, 31, 62, 125, 250 or 500 mg/kg bw/day. Mortalities occurred in all rats and mice at the highest dose. At the 2 highest doses, inactivity and piloerection were observed in both rats and mice. Additionally, rats developed laboured breathing and diarrhoea and at necropsy, gross dark red areas were observed in the stomachs of 3 animals/sex at 500 mg/kg bw/day (NTP, 1983). Further gavage studies with allyl isovalerate were conducted in the same strains of rats (up to 250 mg/kg bw/day) and mice (up to 125 mg/kg bw/day), 5 days/week for 2 weeks. The chemical did not cause effects on haematology or bone marrow cellularity. However, 'subtle myelotoxic effects' in mice and hepatotoxicity in rats were reported (IARC, 1999).

In a 2-year carcinogenicity study, allyl isovalerate was administered to rats and mice in corn oil by gavage at 0, 31 or 62 mg/kg bw/day. In rats, non-neoplastic lesions observed included cholangiofibrosis, cirrhosis, nodular regeneration, focal necrosis, fatty changes and cytoplasmic vacuolisation. Extensive periportal fibrosis was observed in the livers of some high-dose rats, but these effects did not lead to an increase in liver neoplasms (see **Carcinogenicity** section). In mice, no treatment-related non-neoplastic lesions were observed (NTP, 1983).

Similar effects were seen for the 2 structurally similar chemicals, allyl hexanoate and allyl heptanoate. Studies for allyl hexanoate are conducted prior to publication of the OECD test guidelines. In an 18-week study, Osborne-Mendel rats ($n = 10/\text{sex}/\text{dose}$) were administered (by gavage) allyl hexanoate at 0, 15, 65, or 100 mg/kg bw/day. In the high dose groups, liver effects including slight to moderate bile duct proliferation, lobular architectural disarrangement, slight fibrosis, pigment deposition in macrophages and necrotic foci were observed. The NOAEL was reported at 15 mg/kg bw/day (REACHa).

In 2 studies ranging from 13–14 weeks, Wistar rats ($n = 10\text{--}15/\text{sex}/\text{dose}$) were administered (by gavage) allyl hexanoate at doses 0 or 12, or 0, 35 or 100 mg/kg bw/day. Increased incidence of periportal vacuolation in the liver were observed at ≥ 12 mg/kg bw/day, and all treated animals displayed increased relative liver weights at 35 mg/kg bw/day. At the highest dose, bile duct proliferation, hepatocyte enlargement, focal periportal necrosis and increased relative weights of the spleen, kidneys, stomach and small intestine were observed. A NOAEL could not be determined based on liver effects seen at the lowest administered dose (REACHa).

In 2 repeat dose oral toxicity studies where allyl hexanoate was administered in the diet, no adverse effects were observed up to 215 mg/kg bw/day. Osborne-Mendel rats ($n = 5/\text{sex}/\text{dose}$) were administered allyl hexanoate at 1000 ppm (~ 50 mg/kg bw/day) for 28 weeks, or 2500 ppm (~ 215 mg/kg bw/day) for 52 weeks. No adverse effects were observed on body weight, food consumption, general condition or haematological parameters (JECFA, 1991; REACHa).

In a 90-day repeat dose oral toxicity study (OECD TG 408), Wistar rats were administered allyl heptanoate in the diet at 0, 100, 400 or 1500 ppm ($\sim 6.37\text{--}6.85$, $24.43\text{--}27.05$, $84.25\text{--}93.08$ mg/kg bw/day). There were no mortalities and no treatment-related effects in haematological parameters, clinical biochemistry, urinalysis parameters, histopathological and behaviour. At ≥ 400 ppm, the mean body weights, body weight gain and food consumption were significantly lower in both sexes. Decreased organ weights were observed at 1500 ppm (pituitary and thyroid with parathyroid weights for males, kidney and lung weights for females) and at doses ≥ 400 ppm (liver, heart, thymus (both sexes), kidneys, lungs, prostate, spleen (males), and thymus (females)). The changes observed were completely reversible at the end of the recovery period and were correlated to decreased body weight. The NOAEL for systemic toxicity was determined as ≥ 1500 ppm (84.25 (males) and 93.08 mg/kg bw/day (females)) (REACHb).

In a 28-day repeat dose oral toxicity study (OECD TG 407), CD rats were administered (gavage) allyl heptanoate at 0, 10, 30 or 100 mg/kg bw/day, followed by a recovery period of 2 weeks. At the highest dose, treatment-related observations of the liver included yellow-stained discolouration and histopathological changes (chronic inflammation, oval cell hyperplasia and multifocal pigment deposition). All effects had nearly subsided at the end of the recovery period. The no observed effect level (NOEL) was determined as 30 mg/kg bw/day (REACHb).

In a 1 year study (non-guideline), Osborne-Mendel rats (n = 5) were administered allyl cyclohexanepropionate in the diet at 2500 mg/kg bw/day (actual dose = 214 mg/kg bw/day). No adverse effects were observed. In a 27–28 week feeding study, administration of the chemical at 1000 ppm (actual dose = 86 mg/kgbw/day) did not cause any effects in groups of five weanling Osborne-Mendel rats (REACHg).

No hepatotoxicity was observed in a 13-week study in rats administered allyl propionate in the diet at 18 mg/kg bw/day, and in a 17-week study in rats administered allyl butyrate by gavage at 50 mg/kg bw/day. The only effect reported for allyl butyrate was slight to marked peribronchial lymphocytic infiltration of the lungs (WHO, 1997).

Metabolites

In a subchronic toxicity study allyl alcohol was administered to 10 male and female mice (B6C3F1) per group at dose levels of 0, 3, 6, 12, 25 or 50 mg/kg bw/day. In the 50 mg/kg male and 25 mg/kg female dosed groups, a significant increase in the incidence of portal cytoplasmic vacuolisation in the liver (when compared to the control group) was observed. In the 50 mg/kg group, 1 male and 1 female displayed haemosiderin pigmentation. One 50 mg/kg dosed female also showed granulomatous inflammation and hepatocyte necrosis. There was a significant increase in the incidence of squamous epithelial hyperplasia in the forestomach of both males and females dosed with 12, 25 and 50 mg/kg, when compared to the vehicle control group. The LOAEL was 12 mg/kg, based on forestomach squamous epithelial hyperplasia. The NOAEL was 6 mg/kg (REACHc).

In a standard 90-day rat oral study with the metabolite acrolein, no mortalities were observed at dose levels of less than 10 mg/kg bw/day. No significant treatment-related changes or mortalities were observed in mice and dogs, or in rats dosed orally for longer treatment periods with acrolein (CLH, 2011).

Acetic acid and isovaleric acid have been shown to have low systemic toxicity (NICNASc; REACHe). In a poorly guidelineed study, sodium isovalerate did not cause any local or systemic adverse effects in rats when administered in diet over a 3 month period (NOAEL >2000 mg/kg bw/day) (REACHe). Isovaleric acid is associated with toxicity effects in humans with isovaleric acidemia (lethargy, coma, pancytopenia, and ketoacidosis). These effects were not observed in animal studies (NTP, 1983).

Propanoic acid and butyric acid were not toxic following repeated oral exposure (NICNASd, NICNASe).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

There are reported data of haematopoietic toxicity in humans caused by isovaleric acid. Isovaleric acidemia or “sweaty-feet syndrome” caused by a deficiency in the enzyme isovaleryl-CoA dehydrogenase is generally found in neonates. The systemic accumulation of isovaleric acid causes lethargy, pancytopenia, ketoacidosis and coma, but these effects are not observed in rats and mice (CaEPA, 2002).

Genotoxicity

The chemicals were tested for genetic toxicity in bacterial, insect, and mammalian cell systems. Positive results were observed with allyl isovalerate in cytogenetic tests in hamster cells and in a mutagenicity test in mouse cells, without metabolic activation. Negative results were observed with allyl hexanoate, allyl heptanoate (with or without metabolic activation), and allyl acetate (without metabolic activation). Allyl isovalerate, allyl acetate and allyl hexanoate were non-mutagenic in in vivo micronucleus assays. Overall, the results do not indicate mutagenic potential for these chemicals.

In vitro

The following results were reported in various in vitro assays for allyl acetate (NTP, 1993; NTP, 2006):

- positive in bacterial reverse mutation assays with strains of *Salmonella typhimurium* (TA100 and TA1535) up to 3333 µg/plate without metabolic activation; but negative in these strains with metabolic activation presumably due to hydrolysis to allyl alcohol. The chemical was negative in strains TA97 and TA98, with or without metabolic activation;
- negative for mitotic gene conversion in *Saccharomyces cerevisiae* strain JD1; and
- negative in a rat liver chromosomal aberrations (CA) test.

The following results were reported in various in vitro assays for allyl hexanoate (JECFA, 1991; REACHa):

- negative in bacterial reverse mutation assays with several strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538) at concentrations up to 3.5 mg/plate, with or without metabolic activation;
- not mutagenic in vitro micronucleus test in human lymphocytes when tested up to cytotoxic concentrations; and
- negative in the mammalian cell HPRT gene mutation assay in Chinese hamster lung (V79) fibroblasts, with or without metabolic activation.

The following results were reported for allyl heptanoate (REACHb):

- in bacterial reverse mutation assays in various strains of *S. typhimurium* (TA98, TA100, TA102, TA1535 and TA1537), allyl heptanoate was mutagenic at 500 µg/plate in all strains in the absence of metabolic activation, and was mutagenic in strains TA98 and TA1535 at 50 µg/plate and in the strains TA100, TA102, and TA1537 at 150 µg/plate with metabolic activation (REACHb). However, the results were not statistically significant.

The following results were reported in various in vitro assays for allyl isovalerate (JECFA, 1991; IARC, 1999; CalEPA, 2002):

- negative in bacterial reverse mutation assays with several strains of *S. typhimurium* (TA98, TA100, TA1535 and TA1537) at concentrations up to 500 µg/mL, with or without metabolic activation;
- induced sister chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells, weakly with metabolic activation, and more strongly without metabolic activation at 250 µg/mL. However, this occurred at cytostatic doses;
- induced chromosomal aberrations (CA) in CHO cells with metabolic activation at 300–500 µg/mL (NTP, 1983). A recent test showed positive results at concentrations <100 µg/mL, with metabolic activation (Kirkland and Fowler, 2010);
- positive in a mouse lymphoma forward mutation assay in L5178Y cells at 100 µg/mL without metabolic activation; and
- negative in a mammalian cell transformation assay in BALB/c-3T3 cells up to 0.7 mM (Matthews et al., 1993).

The following results were reported in various in vitro assays for allyl cyclohexanepropionate (REACHg):

- negative in bacterial reverse mutation assays with several strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538) at concentrations up to 3.6 mg/plate, with or without metabolic activation;
- negative in a mammalian cell micronucleus test in human lymphocytes when tested up to the highest required or evaluable concentration (1963 µg/mL or 10 mM), with or without metabolic activation;

negative in a mammalian cell HPRT gene mutation assay in V79 fibroblasts, with or without activation.

In vivo

Allyl acetate did not induce micronucleated erythrocytes in a bone marrow micronucleus test in male rats administered the chemical by gavage at doses up to 300 mg/kg bw 3 times, every 24 hours. For mice administered (gavage) allyl acetate up to 62.5 mg/kg bw/day for 14 weeks, a small but significantly increased frequency of micronucleated normochromatic erythrocytes (NCEs) was observed in the peripheral blood of females, but no significant effect was observed in males (NTP, 2006).

Allyl isovalerate did not induce sex-linked recessive lethal mutations in adult *Drosophila melanogaster* exposed by feed or injection (CalEPA, 2002).

Allyl hexanoate was not mutagenic in an in vivo mouse bone marrow micronucleus assay when tested under non-GLP conditions according to OECD Test Guideline (TG) 475 (REACHa). Male and female NMRI mice were administered the

chemical at 39, 78 and 156 mg/kg bw by intraperitoneal injection at 0 and 24 hours. A total of 1000 polychromatic erythrocytes from each animal was analysed for micronuclei. The results were expressed as mean number of micronucleated polychromatic erythrocytes (MNPE) per 1000 polychromatic erythrocytes (PE). The results observed in the treated animals were not statistically different from the controls (2.2/1000, 3.7/1000, 2.5/1000 at 0, 39 and 78 mg/kg bw, respectively).

Similar to the test for allyl hexanoate, allyl cyclohexanepropionate was not mutagenic in the mouse bone marrow micronucleus assay (OECD TG 475), when tested at 49, 78 and 156 mg/kg bw in NMR1 mice. The mean number of MNPE reported were 2.2/1000, 1.8/1000, 1.7/1000 and 4.0/1000 at 0, 49, 78 and 156 mg/kg bw, respectively (REACHg).

Metabolites

Via enzymatic metabolism, allyl esters are metabolised to allyl alcohol, which is then converted to the highly toxic, α,β -unsaturated aldehyde, acrolein. Acrolein can be further oxidised to acrylic acid, conjugated to glutathione, or react with cellular macromolecules to cause toxicity and to the epoxides glycidol and glycidaldehyde (see **Toxicokinetics** section). Notably, the toxicity of allyl esters are correlated with hydrolysis to allyl alcohol and subsequent conversion to acrolein. Therefore, mutagenicity and DNA reactivity of these chemicals will be related to their ability to form their metabolites (Auerbach et. al., 2008).

Allyl alcohol was not mutagenic in *S. Typhimurium* (TA97, TA98, TA100 and TA1535), with or without metabolic activation. The in vivo results were similar to allyl acetate: allyl alcohol did not significantly increase micronucleated erythrocytes in the bone marrow of male rats administered the chemical intraperitoneally (i.p.) at doses up to 40 mg/kg bw, and did not increase frequencies of NCEs in the peripheral blood of male or female mice administered the chemical at doses up to 50 mg/kg bw/day for 14 weeks. There were no effects on the percentage of PCEs (NTP, 2006).

Acrolein induced DNA adducts in a variety of cell types, gave positive results in *Salmonella*, and sister chromatid exchanges (SCE) induction in Chinese hamster ovary (CHO) cells without S9. It did not induce CA in CHO cells. Acrolein was negative in *Drosophila* and did not induce dominant lethal mutation in mice (NTP, 2006). Positive results were generally observed in a narrow, near lethal, dose range (US EPA, 2003). Evidence for carcinogenicity in animals and humans were considered inadequate (NTP, 2006). Acrolein is an alkylating agent and; therefore, a direct-acting mutagen. Acrolein was a mutagen for bacteria and induced gene mutations and sister chromatid exchanges, but showed negative results in chromosome aberrations test in mammalian cells. The mutagenicity of acrolein in bacteria and mammalian cells in vitro was observed at a narrow dose range that was near to or overlapped with the cytotoxic dose range. Acrolein did not induce DNA damage or mutations in fungi. Acrolein appeared genotoxic in the 'somatic mutation and recombination test' in *D. melanogaster*, but did not exhibit genotoxic activity in the 'sex chromosome loss test', while equivocal results were obtained in the 'sex-linked recessive lethal test' in *D. melanogaster*. Acrolein did not induce dominant lethal mutations in mice or chromosome aberrations in bone marrow cells of rats (NTP, 2006; OECD, 2016). Additionally, the metabolism of allyl esters can produce higher internal dose levels of acrolein-GSH adducts, increasing the risk of glycidaldehyde formation (Auerbach et. al., 2008). Both glycidol and glycidaldehyde are known mutagens. The reactive epoxide moiety in glycidol is attributed to genotoxic activity without metabolic activation (CaI EPA, 2002). Glycidol is a classified genotoxic carcinogen (NICNASb), however, the amount formed following metabolism of the esters is unknown.

QSAR

Using the Organisation for Economic Cooperation and Development (OECD) Toolbox (version 3.4), QSAR modelling gave a structural alert for protein binding, based on activated alkyl esters and thioesters. The suggested mechanism for protein reactivity is nucleophilic substitution on an activated carbon atom, which in this case, is the allyl moiety of the compound. Allyl phenylacetate has an additional alert for DNA binding, based on a P450 mediated activation to quinones via a Michael addition mechanism. Using OASIS-TIMES (version 2.27.19), QSAR modelling resulted in a negative prediction as a mutagen for the parent, and positive prediction as a mutagen for the metabolite. However, the chemical structure was out of the applicability domain for all models, indicating uncertainty about the reliability of the results.

Carcinogenicity

Only data on allyl isovalerate are available. The mechanism of action for carcinogenicity of the chemicals is not completely understood; although both genotoxic and non-genotoxic modes of action are considered plausible. The formation of reactive species that are capable of binding to glutathione, or react with cellular macromolecules to cause toxicity is another likely possibility. Results from a two-year carcinogenicity study suggested that allyl isovalerate caused increased incidence of haematopoietic system neoplasms (mononuclear cell leukaemia in male rats and malignant lymphomas in female mice).

However, there is a lack of evidence of carcinogenicity from the metabolites (except glycidol) or the structurally similar esters. In the absence of more comprehensive information, no classification is recommended. If further data becomes available, the need for classification can be revised.

In a two-year carcinogenicity study conducted by the NTP, B6C3F1 mice and F344/N rats (n = 50/sex/dose) were administered allyl isovalerate in corn oil by gavage at 0, 31 or 62 mg/kg bw/day, 5 times/week for 103 weeks. Survival and mean body weight gain in the animals were not adversely affected by the treatment. Squamous cell papillomas of the gastric mucosa (0/50, 1/50, 3/48 for 0, 31 or 62 mg/kg bw/day, respectively) and squamous cell hyperplasia of the forestomach (1/50, 1/50, 7/48 for 0, 31 or 62 mg/kg bw/day, respectively) were significantly increased in male mice. Although not statistically significant, squamous cell papillomas (1/50, 0/50, 2/50) and epithelial hyperplasia of the nonglandular stomach (0/50, 2/50, 3/50) were also observed in female mice. Pancreatic acinar-cell adenomas occurred at higher incidences in the dosed male rats (1/50, 4/50, 2/50) but not in female rats. Preputial gland adenomas were observed in increased incidence in low-dose male rats (0/50, 4/50, 1/50). Mononuclear-cell leukemias in male (1/50, 4/50, 7/50) and female (4/50, 6/50, 9/50) rats, and lymphomas in male (4/50, 6/50, 8/50) and female (11/50, 11/50, 18/50) mice occurred with increased incidences. Cholangiofibrosis, nodular regeneration, cirrhosis, focal necrosis, fatty metamorphosis, and cytoplasmic vacuolisation were observed at increased incidences in the livers of high-dose male and female rats in the 2-year study. No compound-related nonneoplastic lesions were observed in the mice of either sex. Liver neoplasms were not increased in either dosed rats or mice of either sex. Significant decreases in tumour incidences were observed in male mice for hepatocellular carcinomas (18/50, 6/50, 9/50) and alveolar/bronchiolar adenomas or carcinomas (13/50, 6/50, 5/49) and for follicular cell adenomas of the thyroid gland (5/47, 0/46, 1/49). The NTP concluded that the chemical was carcinogenic under the conditions of these studies, based on increased incidence of haematopoietic system neoplasms (mononuclear cell leukaemia in male rats and malignant lymphomas in female mice) (NTP, 1983).

The International Agency for Research on Cancer (IARC) has classified allyl isovalerate as 'not classifiable as to its carcinogenicity to humans' (Group 3), based on no epidemiological data relevant for carcinogenicity in humans, and limited evidence for carcinogenicity in animal testing seen in the NTP study discussed above (IARC, 1999).

Metabolites

Allyl alcohol was tested in a 48-week chronic/carcinogenicity study in male hamsters at gavage doses of 2 mg/week. No forestomach or pancreas tumours were observed; however, adenomas or carcinomas of the adrenal cortex were observed in four out of 13 survivors. Allyl alcohol administered at 300 ppm in drinking water to F344 rats up to 126 weeks did not show increased incidences of neoplastic changes compared with the controls (HSDB).

The carcinogenic potential of acrolein has been investigated in lifetime gavage studies in rats and mice, and no treatment-related increases in tumour incidence were observed (CLH, 2011; REACHc). Although incidences of mammary neoplasms and neoplastic pancreatic lesions were observed these occurred within historical limits and were not considered to be dose related. No significant increase in the incidence of microscopic lesions (neoplastic or non-neoplastic) was observed in rats treated with acrolein.

The metabolite, glycidol is classified as hazardous with hazard category 'Category 2 carcinogen' and hazard statement 'Suspected of causing cancer - Cat. 2 (H315)' in HCIS (Safe Work Australia) (NICNASb).

Reproductive and Developmental Toxicity

Based on the data available for allyl heptanoate, allyl cyclohexanepropionate, and the immediate metabolite acrolein, the chemicals in this group are not likely to be reproductive or developmental toxicants.

In a reproductive and developmental study (OECD TG 421), allyl heptanoate was administered (gavage) to Crj: CD(SD) rats (n = 10/sex/dose) at 0, 10, 30 or 100 mg/kg bw/day during the pre-mating and mating periods to parental males; and during the pre-mating, mating, gestation and lactation periods until day 3 postpartum to parental females. In parental animals (P0) at ≥ 30 mg/kg bw/day, macroscopic changes observed included white flocculation in the urinary bladder in males, and effects on the liver (thickening, yellow foci, yellowish discolourations) and thickened spleen in females. At the highest dose, the mean body weights of female rats were slightly increased during the pre-mating and gestation period. No treatment-related effects on the reproductive performance of P0 were observed. For the offspring (F1), no treatment-related effects were observed at any of the treated doses on the growth and development of the offspring from conception to day 4 postpartum. The NOELs for developmental toxicity for P0 and F1 were 10 and ≥ 100 mg/kg bw/day, respectively (REACHb).

In a developmental study (OECD TG 414), groups of Wistar rats (n = 24/sex/dose) were administered allyl heptanoate in the diet at 0, 100, 400 or 1500 ppm (~6.95, 25.71 and 77.40 mg/kg bw/day) on gestation days (GD) 5–20. For the parental animals, a significant reduction in intermittent body weight gains and maternal body weight gain, reduction in food intake (due to palatability) were observed. There were no treatment-related effects on maternal developmental parameters and on the fetuses. The NOAEL was determined as ≥ 1500 ppm in this study (REACHb).

Allyl cyclohexanepropionate was tested in a one-generation reproductive toxicity study (OECD TG 415) in SD rats at 0, 75, 125, 250 or 500 mg/kg bw/day. The parental animals were administered the chemical during pre-mating, mating, gestation and lactation periods. At ≥ 250 mg/kg bw/day, decreased motor activity, slight excess salivation, mild dehydration, abnormal faecal output, hunched posture, and decreased body weight gain were observed. Mating and fertility parameters were unaffected up to 125 mg/kg bw/day. Abnormal oestrous cycles were observed in two female rats at 250 mg/kg bw/day. Multifocal necrosis, periportal vacuolation of hepatocytes and cholangiofibrosis were observed in the livers of the parental animals at all treated groups. No significant effects were seen in the offspring. The NOAELs for general toxicity and reproductive toxicity were <75 mg/kg bw/day and 125 mg/kg bw/day, respectively (REACHg).

The immediate metabolite acrolein did not cause effects on reproductive parameters (mating performance and fertility indices) in a 2-generation oral reproductive study in SD rats, except for a slight reduction in F1 pup weights at 6 mg/kg bw. The NOAEL was established at 3 mg/kg bw for developmental and 1 mg/kg bw per day for parental effects. In an oral developmental study in pregnant NZW rabbits, the NOAEL was established at 2 mg/kg bw or higher for developmental and 0.75 mg/kg bw per day for maternal effects. Developmental effects in mammals in vivo were only seen at dose levels that also resulted in maternal toxicity (US EPA, 2003).

The metabolite, glycidol is classified as hazardous as a Category 2 substance toxic to reproduction with the risk phrase 'May impair fertility' (T; R60) HCIS (Safe Work Australia). There were several studies in rats and mice indicating reproductive toxicity effects (NICNASb). However the concentration of glycidol formed following metabolism of the esters is unknown.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

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

Allyl acetate (CAS No. 591-87-7) may cause local effects (corrosivity) and systemic long-term effects (repeated dose toxicity).

Public Risk Characterisation

In Australia, the chemicals allyl hexanoate (CAS No. 123-68-2) and allyl cyclohexanepropionate (CAS No. 2705-87-5) have reported domestic and commercial uses in automobile products. The chemicals in this group are also 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, as derivatives, the chemicals fall within the scope of the listing of 'allyl alcohol' in Schedule 7 of the SUSMP. It is recommended that 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 low concentration cut-off consistent with IFRA controls 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 long-term and 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) (see **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 these chemicals 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.

The following amendments to the SUSMP are recommended:

- amend the entry for allyl alcohol in schedule 7 to exclude its derivatives, and to allow low levels as an impurity in allyl esters; and
- create a new entry in a lower schedule for allyl esters.

Regulatory Control

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 corrosivity and repeat dose toxicity classification applies to allyl acetate (CAS No. 591-87-7) only.

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 | Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) |
| Irritation / Corrosivity | Not Applicable | Causes severe skin burns and eye damage - Cat. 1 (H314) |
| Repeat Dose Toxicity | Not Applicable | May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373) |

^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 these chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to these 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;
- 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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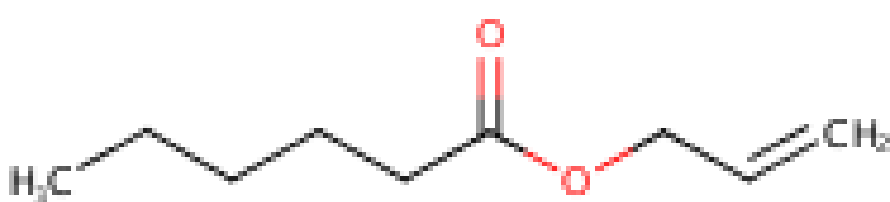
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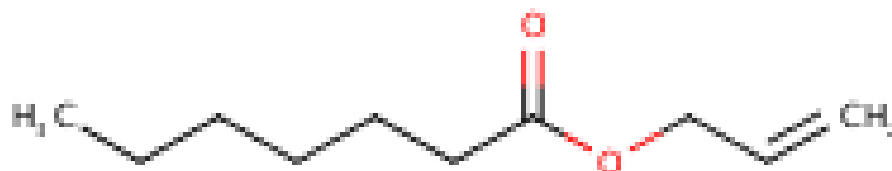
Chemical Identities

| | |
|---|--|
| Chemical Name in the Inventory and Synonyms | Butanoic acid, 2-propenyl ester allyl butyrate |
| CAS Number | 2051-78-7 |
| Structural Formula | |
| Molecular Formula | C7H12O2 |
| Molecular Weight | 128.17 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | Hexanoic acid, 2-propenyl ester 2-propenyl hexanoate allyl caproate allyl hexanoate |
|---|---|

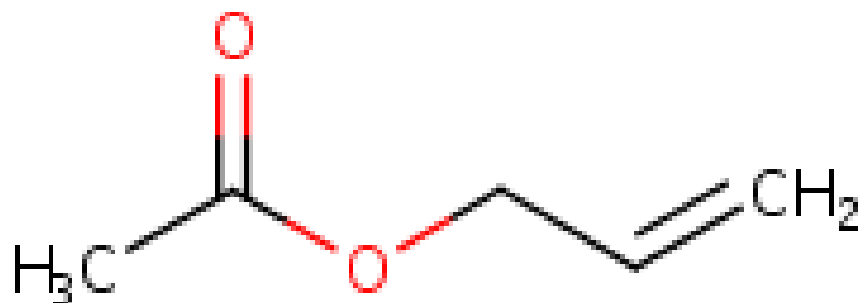
| | |
|--------------------|---|
| CAS Number | 123-68-2 |
| Structural Formula |  <p>The structural formula shows a heptanoate chain (a seven-carbon chain with a terminal methyl group labeled H₃C) connected via an ester linkage to an allyl group (a three-carbon chain with a terminal methylene group labeled CH₂ and a double bond between the second and third carbons). The oxygen atoms in the ester linkage are highlighted in red.</p> |
| Molecular Formula | C ₉ H ₁₆ O ₂ |
| Molecular Weight | 156.22 |

| | |
|---|--|
| Chemical Name in the Inventory and Synonyms | Heptanoic acid, 2-propenyl ester allyl heptanoate allyl heptylate |
| CAS Number | 142-19-8 |
| Structural Formula | |



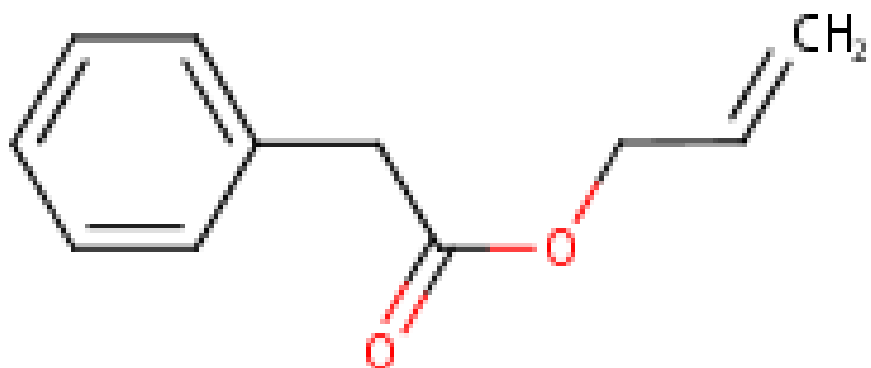
| | |
|-------------------|--|
| Molecular Formula | C ₁₀ H ₁₈ O ₂ |
| Molecular Weight | 170.25 |

| | |
|---|--|
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| CAS Number | 591-87-7 |
| Structural Formula | |



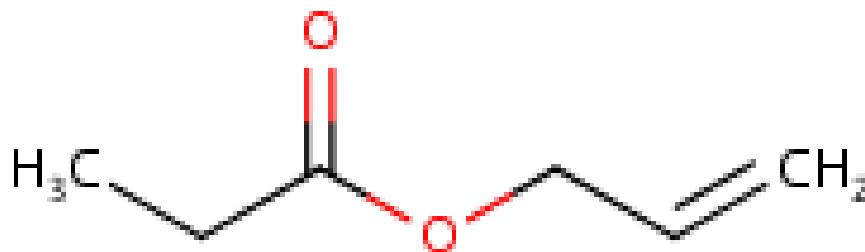
| | |
|-------------------|--|
| Molecular Formula | C ₅ H ₈ O ₂ |
| Molecular Weight | 100.12 |

| | |
|---|--|
| Chemical Name in the Inventory and Synonyms | Benzeneacetic acid, 2-propenyl ester allyl phenylacetate 2-propenyl benzeneacetate allyl alpha-toluate |
| CAS Number | 1797-74-6 |
| Structural Formula | |



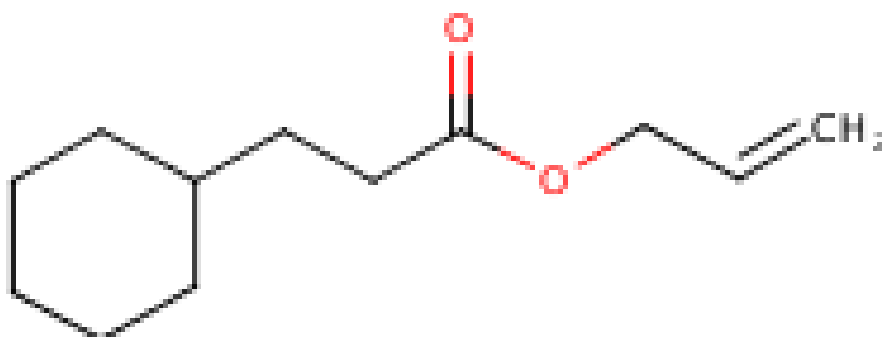
| | |
|-------------------|----------|
| Molecular Formula | C11H12O2 |
| Molecular Weight | 170.21 |

| | |
|---|---|
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| CAS Number | 2408-20-0 |
| Structural Formula | |



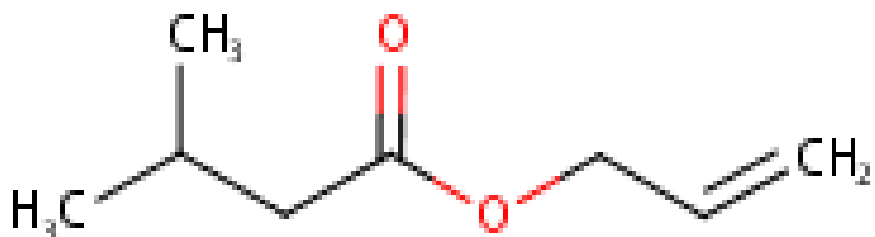
| | |
|-------------------|---------|
| Molecular Formula | C6H10O2 |
| Molecular Weight | 114.14 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | Cyclohexanepropanoic acid, 2-propenyl ester allyl cyclohexanepropanoate allyl hexahydrophenylpropanoate allyl cyclohexyl propanoate |
| CAS Number | 2705-87-5 |
| Structural Formula | |



| | |
|-------------------|--|
| Molecular Formula | C ₁₂ H ₂₀ O ₂ |
| Molecular Weight | 196.29 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | Butanoic acid, 3-methyl-, 2-propenyl ester allyl isovalerate 2-propenyl 3-methylbutanoate butyric acid, 3-methyl-, allyl ester allyl isopentanoate 2-propenyl isovalerate |
| CAS Number | 2835-39-4 |
| Structural Formula | |



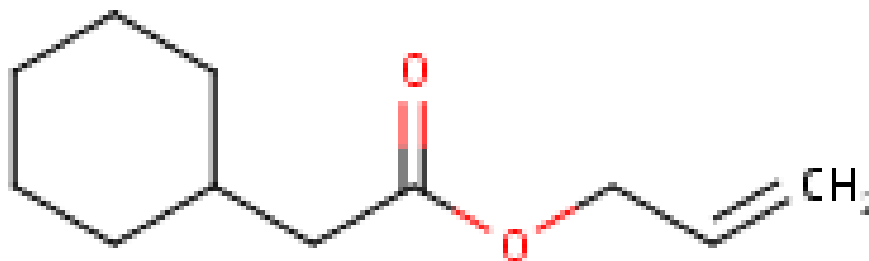
| | |
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| Molecular Formula | C ₈ H ₁₄ O ₂ |
| Molecular Weight | 142.2 |

| | |
|---|--|
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| CAS Number | 4230-97-1 |
| Structural Formula | |



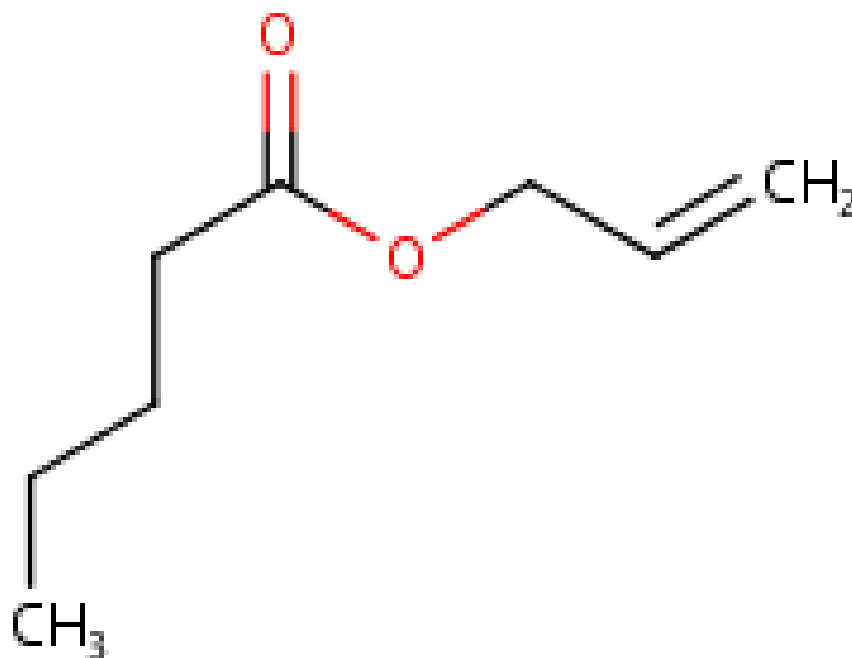
| | |
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| Molecular Formula | C ₁₁ H ₂₀ O ₂ |
| Molecular Weight | 184.28 |

| | |
|---|--|
| Chemical Name in the Inventory and Synonyms | Cyclohexaneacetic acid, 2-propenyl ester allyl cyclohexaneacetate allyl hexahydrophenylacetate acetic acid, cyclohexyl-, allyl ester |
| CAS Number | 4728-82-9 |
| Structural Formula | |



| | |
|-------------------|----------|
| Molecular Formula | C11H18O2 |
| Molecular Weight | 182.26 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | Pentanoic acid, 2-propenyl ester allyl valerate allyl pentanoate |
| CAS Number | 6321-45-5 |
| Structural Formula | |



| | |
|-------------------|---|
| Molecular Formula | C ₈ H ₁₄ O ₂ |
| Molecular Weight | 142.20 |

| | |
|---|--|
| Chemical Name in the Inventory and Synonyms | Nonanoic acid, 2-propenyl ester nonanoic acid, allyl ester allyl nonanoate allyl oenanthat |
| CAS Number | 7493-72-3 |
| Structural Formula | |



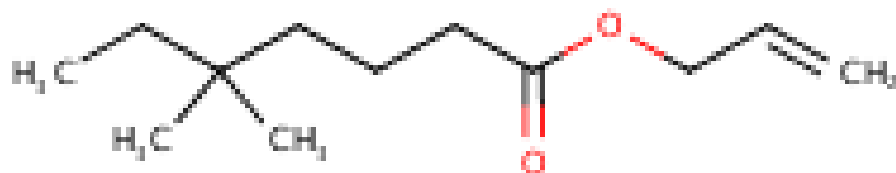
| | |
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| Molecular Formula | C12H22O2 |
| Molecular Weight | 198.30 |

| | |
|---|--|
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| CAS Number | 57856-81-2 |
| Structural Formula | |



| | |
|-------------------|--|
| Molecular Formula | C ₁₃ H ₂₄ O ₂ |
| Molecular Weight | 212.33 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | Hexanoic acid, trimethyl-, 2-propenyl ester allyl trimethylhexoate allyl isononylate allyl trimethylhexanoate |
| CAS Number | 68132-80-9 |
| Structural Formula | |



| | |
|-------------------|--|
| Molecular Formula | C ₁₂ H ₂₂ O ₂ |
| Molecular Weight | 198.30 |

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