Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Octynoic and nonynoic acid esters

Evaluation statement

28 January 2022

Draft

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Subject of the evaluation

Octynoic and nonynoic acid esters

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2-Nonynoic acid, 2-methylpropyl ester	84282-44-0

Reason for the evaluation

The evaluation selection analysis indicated a potential risk to human health.

Parameters of evaluation

The chemicals are esters of octynoic acid and nonynoic acid listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses (except use in e-cigarettes due to absence of relevant hazard data) of the chemicals in this group of structurally similar esters. All chemicals in this group have an electrophilic α,β-unsaturated ester group with the ability to react with proteins. These chemicals have been assessed as a group as they are expected to have similar toxicity and bioavailability.

Summary of evaluation

Summary of introduction, use and end use

There is no specific information about the introduction, use and end use of the chemicals in Australia.

Methyl 2-octyonate and methyl 2-nonyoate are used as fragrance ingredients in cosmetic and domestic products. Based on international use information, they are used in personal care and air freshener products, polishes and waxes, and washing and cleaning products (DeLima Associates; REACHa; REACHb).

In Europe, the use of methyl 2-octyonate and methyl 2-nonyoate in cosmetic products is restricted to a maximum allowable concentration of 0.01% and 0.002% in finished products, respectively (EC). Reported use concentrations of methyl 2-octyonate and Methyl 2-nonyoate are 0.007% and 0.006%, respectively (95th percentile) (Api et al. 2019a; Api et al. 2019b; Lim et al. 2018).

The use of methyl 2-octyonate and methyl 2-nonyoate is expected to be widespread as it is present in various types of cosmetic and domestic products. Limited use information is available for the other chemicals in this group. They are prohibited for use as fragrances under the IFRA standard and are; therefore, expected to have less widespread use.

Human health

Summary of health hazards

The critical health effect for risk characterisation is the local effect of skin sensitisation.

The chemicals are expected to be strong sensitisers based on animal and human data. In local lymph node assay (LLNA) studies, reported concentrations producing a 3 fold increase in lymphocyte proliferation (EC3) for methyl 2-octyonate and methyl 2-nonyoate were of 0.45% (112 µg/cm^2) and 2.5% (625 µg/cm^2), respectively. However, the EC3 of 2.5% for methyl 2-nonyoate was not confirmed in a human repeated insult patch test (HRIPT) which showed positive reactions at 118 µg/cm^2 (equivalent to an EC3 value of approximately 0.5%). Methyl 2-octynaote is an established human contact allergen. The frequency of reactions is higher in specific groups with suspected cosmetic or fragrance allergy.

The chemicals have low acute oral toxicity based on animal data, with median lethal doses (LD50) of >2000 mg/kg bw in rats. There was no information on acute dermal toxicity or acute inhalation toxicity of the chemicals.

Based on the limited available data for methyl 2-nonynoate and methyl 2-octynoate, these chemicals may be slightly irritating to skin. No information is available for other chemicals in this group.

There are no experimental data available on the repeat dose toxicity, carcinogenicity and reproductive toxicity endpoints for the chemicals.

Based on the weight of evidence of in vitro, in vivo and in silico data, the chemicals are not expected to be genotoxic.

Health hazard classification

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

Some of these recommended classifications are based on read across principles (see **Supporting Information – Grouping rationale** section). If empirical data become available for any member of this group indicating that a lower (or higher) classification is appropriate for a specific chemical, that data may be used to amend the default classification for that chemical.

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin Sens. 1A	H317: May cause an allergic skin reaction

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemicals by:

- direct application of the chemicals to the skin or hair
- direct skin contact during use of domestic products
- incidental skin and eye contact with the chemicals during use of domestic products
- inhaling aerosols.

There is potentially widespread public exposure, to methyl 2-octyonate and methyl 2-nonyoate, which are expected to be present in various types of domestic and cosmetic products. The chemicals in the group are expected to be strong skin sensitisers. The use of the chemicals are expected to be controlled by members of IFRA through application of concentration limits in fragrance products. However, a quantitative risk assessment undertaken by AICIS as part of this evaluation (see **Supporting information** section) established an acceptable exposure concentration (AEC) of 0.01%. Therefore, the IFRA concentration limit of 0.047% for methyl 2-octyonate in fine fragrances may not be sufficient to manage the risk of induction of skin sensitisation.

Given the identified health hazard, the local effect of skin sensitisation, the evidence indicates that there is a risk to the public that requires management (see **Proposed means for managing any risks** section). The risk could be managed by including these chemicals in the Poisons Standard. Although there is no information regarding the systemic effects of these chemicals, controls implemented due to the sensitisation potential of the chemicals will minimise systemic exposure and; hence, any potential systemic effects.

Workers

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

Given the critical local health effects, these chemicals could pose a risk to workers.

Control measures to minimise dermal exposure are needed to manage the risk to workers (see **Proposed means for managing any risks** section). Control measures implemented due to the sensitisation classification are expected to be sufficient to protect workers from any potential systemic health effects.

Proposed means for managing risk

Public

It is recommended that the delegate of the Secretary for Poisons Scheduling list these chemicals in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP).

It is recommended that to manage the potential risk associated with the use of these chemicals that the entry:

- restricts the concentration of these chemicals in consumer products.

Consideration should be given to the following:

- the expected use of these chemicals in domestic and cosmetic products available in Australia
- these chemicals are strong sensitisers based on animal and human data
- these chemicals are restricted for cosmetic use overseas. Restrictions on the use of these chemicals in cosmetic products in other countries (see **Restrictions: International** section) are considered appropriate in Australia, to manage the risk
- a quantitative risk assessment as part of this evaluation established an AEC of 0.01%.

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from dermal exposure to these chemicals include, but are not limited to:

- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals, if valid techniques are available to monitor the effect on the worker's health.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this Evaluation Statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

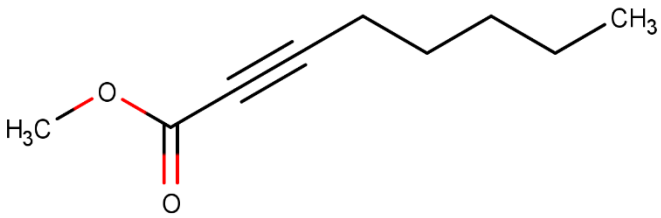
Supporting information

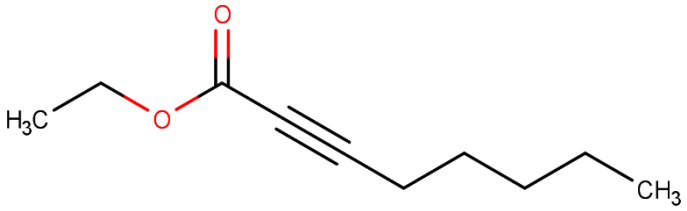
Grouping rationale

The chemicals in this group are structurally similar esters with an electrophilic μ,β-unsaturated ester group that has the ability to react with proteins. These chemicals have been assessed as a group as they are expected to have similar uses, toxicity and bioavailability.

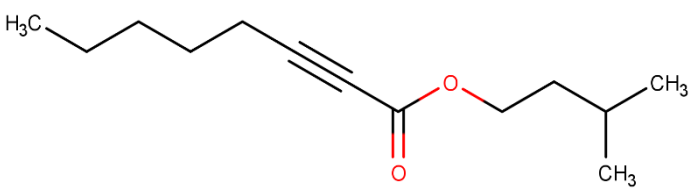
Chemical identity

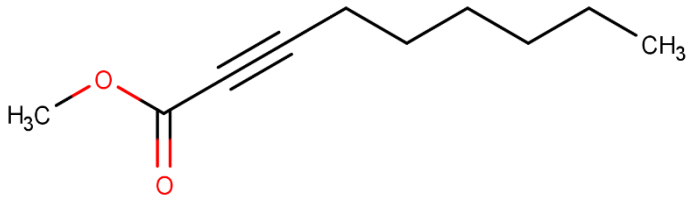
Chemical name	2-Octynoic acid, methyl ester
CAS No.	111-12-6

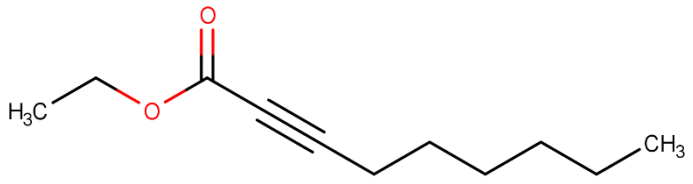
Synonyms	methyl 2-octynoate methyl hept-1-yne-1-carboxylate methyl heptine carbonate
Structural formula	
Molecular formula	C9H14O2
Molecular weight (g/mol)	154.21
SMILES	O=C(C#CCCCCC)OC

Chemical name	2-Octynoic acid, ethyl ester
CAS No.	10519-20-7
Synonyms	ethyl 2-octynoate ethyl heptine carbonate
Structural formula	
Molecular formula	C10H16O2
Molecular weight (g/mol)	168.23
SMILES	O=C(C#CCCCCC)OCC

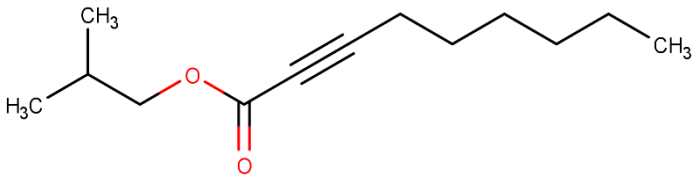
Chemical name	2-Octynoic acid, 3-methylbutyl ester
CAS No.	68555-60-2
Synonyms	isoamyl 2-octynoate isoamyl heptine carbonate

Structural formula	
Molecular formula	C13H22O2
Molecular weight (g/mol)	210.31
SMILES	O=C(C#CCCCCC)OCCC(C)C

Chemical name	2-Nonynoic acid, methyl ester
CAS No.	111-80-8
Synonyms	methyl 2-nonynoate methyl octyne carbonate
Structural formula	
Molecular formula	C10H16O2
Molecular weight (g/mol)	168.23
SMILES	O=C(C#CCCCCCC)OC

Chemical name	2-Nonynoic acid, ethyl ester
CAS No.	10031-92-2
Synonyms	ethyl octine carbonate ethyl non-2-ynoate
Structural formula	
Molecular formula	C11H18O2

Molecular weight (g/mol)	182.26
SMILES	O=C(C#CCCCCCC)OCC

Chemical name	2-Nonynoic acid, 2-methylpropyl ester
CAS No.	84282-44-0
Synonyms	isobutyl non-2-ynoate 2-methylpropyl non-2-ynoate isobutyl octine carbonate
Structural formula	
Molecular formula	C13H22O2
Molecular weight (g/mol)	210.31
SMILES	O=C(C#CCCCCCC)OCC(C)C

Relevant physical and chemical properties

The chemicals in this group have molecular weights ranging from 154.21 to 210.31 g/mol and log Kow values between 3.1 and 4.5. Based on the reported experimental and calculated vapour pressures below 0.5 kPa the chemicals are expected to have low volatility.

Introduction and use

Australia

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

International

The following international uses have been identified through the:

- European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers (REACHa; REACHb)
- US Environmental Protection Agency (EPA) (US EPA 2021)
- Government of Canada (Government of Canada 2021).

Methyl 2-nonynoate and methyl 2-octynoate have reported cosmetic uses as fragrance ingredients.

Reported use concentrations of methyl 2-octyonate and methyl 2-nonyoate are 0.007% and 0.006%, respectively (95th percentile) (Api et al. 2019a; Api et al. 2019b). In a quantitative analysis of fragrance allergens in 107 commercial perfumes for women, the mean concentration of methyl 2-octyonate was 0.007% (median 0.0012%). Concentrations in men's perfumes were lower with a mean of 0.0014% (median not determined) (Lim et al. 2018).

Global volumes of 1–10 and 10–100 t/y were reported for methyl 2-octyonate and methyl 2-nonyoate, respectively (Api et al. 2019a, Api et al. 2019b). Methyl 2-octynoate is listed in the Compilation of Ingredients Used in Cosmetics in the United States (Personal Care Products Council 2011), indicating use in 45 cosmetic products.

Methyl 2-nonynoate and methyl 2-octynoate are listed on the International Fragrances Association (IFRA) transparency list.

Methyl 2-octynoate has reported use in cigarettes and e-cigarettes.

Methyl 2-nonynoate and methyl 2-octynoate have reported domestic uses in:

- cleaning and washing agents
- polishes and waxes
- air freshener products.

The Consumer Product Information Database (CPID) reports concentrations of 0.5–1.5% of methyl 2-octynoate and 0.1–1% methyl 2-nonyoate in air freshener products (non-aerosol) (DeLima Associates).

Methyl 2-octynoate has reported commercial use in car care and metal surface treatment products.

Ethyl 2-nonynoate has reported non-industrial use as a food additive.

No current industrial use information was identified for the other chemicals in this evaluation.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No restrictions for industrial use have been identified for the chemicals in Australia.

Methyl 2-nonynoate and methyl 2-octynoate have restrictions for their non-industrial uses in the *Therapeutic Goods (Permissible Ingredients) Determination No. 3 of 2021* as excipients in medicines (TGA 2021) at certain concentrations depending on their use as a flavour or a fragrance:

Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.

- If used in a flavour, the total flavour concentration in a medicine must be no more than 5%.
- If used in a fragrance, the total fragrance concentration in a medicine must be no more than 1%.

Workers

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (Safe Work Australia).

International regulatory status

European Union

Methyl 2-nonynoate and methyl 2-octynoate are listed in *Annex III of EU Regulation (EC) No.1223/2009* - List of substances which cosmetic products must not contain except subject to the restrictions laid down.

- The concentration of methyl 2-nonynoate in cosmetic products should not exceed 0.002% when used alone. When present in combination with methyl 2-octynoate, the combined level in the finished product should not exceed 0.01% (of which methyl 2-nonynoate should not be more than 0.002%).
- The concentration of methyl 2-octynoate in cosmetic products should not exceed 0.01% when used alone. When present in combination with methyl 2-nonynoate, the combined level in the finished product should not exceed 0.01% (of which methyl 2-nonynoate should not be more than 0.002%).

Methyl 2-octynoate and methyl 2-nonyoate need to be declared as ingredients on the label of cosmetic products according to *Article 6 of the Cosmetic Directive* when concentrations exceeds 0.001% in leave on cosmetic products, and 0.01% in rinse-off cosmetic products (EC).

New Zealand

Methyl 2-nonynoate and methyl 2-octynoate are listed in the *New Zealand Cosmetic Products Group Standard - Schedule 5 - Table 1*: Components cosmetic products must not contain except subject to the restrictions and conditions laid down (same restrictions as EU see above).

Other

Methyl 2-octyonate, methyl 2-nonyoate and esters of 2-octynoic acid and 2-nonyoic acid (except methyl 2-octynoate and methyl 2-nonynoate) are listed in the IFRA Standard.

Maximum concentrations recommended by IFRA for methyl 2-octynoate vary (0.0085–0.33% depending of the product). When used in the same fragrance compound within a specific quantitative risk assessment (QRA) category, the sum total of methyl 2-octynoate and methyl 2-nonynoate contributions must not exceed the maximum permitted level for methyl 2-

octynoate. At the same time, the contribution from methyl 2-nonynoate should always respect the maximum levels permitted in the respective categories as listed in the IFRA Standard for methyl 2-nonynoate.

Maximum concentrations recommended by IFRA for methyl 2-nonynoate vary (0.0019–0.072% depending of the product). When used in the same fragrance compound within a specific QRA category, the sum of total of methyl 2-octynoate and methyl 2-nonynoate contributions must not exceed the maximum permitted level for methyl 2-octynoate. At the same time, the contribution from methyl 2-nonynoate should always respect the maximum levels permitted in the respective categories as listed in the IFRA Standard for methyl 2-nonynoate.

Esters of 2-octynoic acid and 2-nonyoic acid (except methyl 2-octynoate and methyl 2-nonynoate) are prohibited for use as fragrances under the IFRA Standard.

Human exposure

Public

Available international use information indicates that methyl 2-octynoate and methyl 2-nonynoate are widely used in cosmetic and domestic products. The formulations of similar products on the market in Australia are unlikely to be significantly different to those found internationally. Therefore, methyl 2-octynoate and methyl 2-nonynoate are expected to be found in a range of personal care and domestic products for use in Australia. The principal route of exposure will be dermal. Exposure to the chemicals is expected to be restricted by industry complying with the IFRA Standard. Exposure has therefore been estimated based on the highest allowed concentration in fine fragrances of methyl 2-octynoate and methyl 2-nonyoate in the IFRA Standard (Table 1).

Data on typical use patterns of products containing methyl 2-octynoate and methyl 2-nonynoate were derived from published sources (ACI 2010, Cadby et al. 2002, Loretz et al. 2006, SCCS 2012). For the purposes of exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) rate of 100% and a lifetime average female body weight (BW) of 70 kg (enHealth 2012) were used for calculation purposes.

Table 1 Dermal exposure to methyl 2-octynoate and methyl 2-nonyoate in fine fragrances

Chemical	Product type	Amount (mg/day)	IFRA standard limit (%)	Retention factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Methyl 2-octynoate	Fine fragrances	750	0.047	1	0.005
Methyl 2-nonyoate	Fine fragrances	750	0.01	1	0.0011

Health hazard information

Toxicokinetics

No data are available for the chemicals in this group. The chemicals have molecular weights ranging between 154.21 and 210.31 g/mol and are expected to be orally and dermally available (Lipinski et al. 2001).

Acute toxicity

Oral

Based on the limited available data and in silico modelling, the chemicals are unlikely to be acutely toxic via the oral route.

In a non-good laboratory practice (GLP) compliant acute oral toxicity study, Wistar rats (10/sex/dose) were treated with methyl 2-nonynoate (doses not reported) and observed for 14 days. A median lethal dose (LD50) value of 2200 mg/kg bw was reported (REACH).

In a non-GLP compliant acute oral toxicity study with methyl 2-octynoate, an LD50 value of 2500 mg/kg bw was reported (REACH).

The following additional LD50 values were reported (Chemtunes; CCOHS 2021):

- 2850 mg/kg bw in rats (ethyl 2-nonynoate)
- 870 and 2220 mg/kg bw in rats (methyl 2-nonynoate)
- 1530 mg/kg bw in rats (methyl 2-octynoate).

In the Danish (Quantitative) structure activity relationship [(Q)SAR] database (Technical University of Denmark), all of the chemicals were predicted to have LD50 values >2000 mg/kg bw in rats using the Advanced Chemistry Development (ACD) labs acute toxicity model. The prediction quality was considered high based on a reliability score of >0.75.

Dermal

No data are available for the chemicals in this group.

Inhalation

No data are available for the chemicals in this group.

Corrosion/Irritation

Skin irritation

Based on the limited available data for methyl 2-nonynoate and methyl 2-octynoate, the chemicals may be slightly irritating to skin particularly after repeated exposure.

In an open epicutaneous test, application of methyl 2-octynoate (neat) to the skin of guinea pigs resulted in slight skin irritation after 24 hours (REACHa).

In an irritation study similar to an open epicutaneous test, application of methyl 2-nonynoate (neat) to the skin of guinea pigs on 28 consecutive days resulted in slight to moderate skin irritation (REACHb)

In an irritation study, methyl 2-nonynoate (neat) was applied to intact or abraded rabbit skin for 24 hours under occlusion. No irritation was reported (Opdyke et al. 1979)

Eye irritation

Based on the limited data available for methyl 2-nonynoate and methyl 2-octynoate, the chemicals are not considered to cause serious eye damage or eye irritation.

In a GLP compliant ex vivo eye corrosivity/irritation study conducted according to Organisation for Economic Co-operation and Development OECD Test Guideline (TG) 437, methyl 2-octynoate was applied to 3 bovine cornea per experiment. The mean in vitro irritancy score (IVIS) was -1.5 (chemicals with IVIS ≤3 are not classified for eye irritation). Based on the criteria of the assay, the chemical was not considered to be corrosive or a severe irritant to the eye (REACHa).

In a non-GLP compliant eye irritation study, methyl 2-nonynoate was instilled into one eye each of 6 New Zealand White (NZW) rabbits. The reported overall irritation scores were 1 at 24 hours, 0 at 48 hours and 0 at 72 hours (REACHb).

Sensitisation

Skin sensitisation

Based on the available human and animal data the chemicals are expected to be strong sensitisers. The sensitising effects of the esters of octynoic and nonynoic acid can also be synergistic (Heisterberg et al., 2010).

In a non-GLP compliant local lymph node assay (LLNA) similar to OECD TG 429, female CBA mice (4/group) received topical applications of methyl 2-octynoate at 0.05, 0.1, 0.25, 0.5 or 1.0% in 1:3 ethanol/diethyl phthalate, daily, for 3 days. No stimulation index (SI) values were reported. The reported concentration producing a 3fold increase in lymphocyte proliferation (EC3) was 0.45% (112.5 µg/cm^2), indicating strong sensitisation potential. The results from the LLNA was replicated by the research institute for fragrance materials (RIFM) in a second assay (Api et al. 2019a; REACHa).

In a non-GLP compliant LLNA similar to OECD TG 429, female CBA mice (4/group) received topical applications of methyl 2-nonynoate at 5, 10 and 20% in ethanol, daily, for 3 days. The reported SI values were 10.4, 17.7 and 24.4, respectively. The reported concentration producing a 3fold increase in SI was 2.5% (625 µg/cm^2), indicating moderate sensitisation potential (REACHb).

In an open epicutaneous test, 3, 10, 30 or 100% of methyl 2-octynoate in ethanol was applied to guinea pigs (10/dose) 3 times per week for 3 weeks. Skin reactions were reported at all concentrations except at 3% (2/6 at 10%, 5/6 at 30%, 6/6 at 100%) (REACHa).

Methyl 2-nonynoate was found to be positive in an in vitro direct peptide reactivity assay (DPRA), KeratinoSens, a human cell line activation test (h-CLAT), and a U-Sens test (Api et al. 2019b).

Observation in humans

The SCCS (2012) categorised methyl octynoate as an established contact allergen based on reports of between 11 and 100 positive test reactions.

In a human repeat insult patch test (HRIPT) with 118 µg/cm^2 of methyl 2-octynoate in 3:1 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitisation were observed in any of the 104 volunteers (Api et al. 2019a).

In routine patch testing studies in a total of 7257 patients, 0.1–0.2% had positive reactions to methyl 2-octyonate when tested with 1% methyl 2-octyonate in petrolatum (deGroot 2021).

In specific groups with suspected cosmetic or fragrance allergy, the frequency of reactions to methyl 2-octyonate in pet. was generally higher than in routine patch testing studies (Table - 2) (deGroot 2021, Heisterberg et al. 2010).

Table 2 Patch test data for methyl 2-octynoate in patients with confirmed allergy

Number tested	Test concentration	Positive patients (%)
120	2% in pet.	1.67%
708	1% in pet.	0.8%
988	1% in pet.	0.1%
320	1% in pet.	0.3%
230	1% in pet.	0.87%
21	0.5% in pet.	5%
182	0.5% in pet.	1.1%

Limited human data are available for 2-methyl nonynoate. In an (HRIPT) with 118 µg/cm^2 of methyl 2-nonynoate in 3:1 ethanol:diethyl phthalate, reactions indicative of sensitisation were observed in 6/138 volunteers. In an HRIPT at 24 µg/cm^2 of methyl 2-nonynoate in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitisation were reported (Api et al. 2019b).

In2 human maximisation tests, no positive reactions were reported after volunteers (25/study) were exposed to methyl 2-nonynoate at 2% in pet. (Opdyke et al. 1979).

Repeat dose toxicity

Oral

No data are available for the chemicals in this group.

Dermal

No data are available for the chemicals in this group.

Inhalation

No data are available for the chemicals in this group.

Genotoxicity

In vitro

Based on the weight of evidence of in vitro, in vivo and in silico data, the chemicals are not expected to be genotoxic

Negative results were reported in the following in vitro genotoxicity studies for methyl 2-octynoate (REACHa) and methyl 2-nonynoate (REACHb):

- A bacterial reverse mutation assay (OECD TG 471) using methyl 2-nonynoate in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and *Escherichia coli* WP2 uvr A, with and without metabolic activation (S9) (concentrations were not reported).
- A bacterial reverse mutation assay (no guideline reported) using methyl 2-nonynoate in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and *E. coli* WP2 uvr A, with and without metabolic activation (S9) was reported at concentrations up to 3.6 mg/plate.

In vivo

The clastogenic potential of methyl 2-octynoate was assessed in an in vivo micronucleus test similar to OECD TG 474. Groups of male and female (Naval Medical Research Institute) NMRI mice were treated with methyl 2-octynoate in olive oil via a single intraperitoneal injection at concentrations of 168, 336 or 505 mg/kg bw. No significant increase in the number of micronucleated polychromatic erythrocytes was observed (Api et al. 2019a)

In a similar in vivo micronucleus test, mice were administered methyl 2-nonynoate in a single intraperitoneal injection at concentrations of 154, 231 or 308 mg/kg bw. No significant increase in the number of micronucleated polychromatic erythrocytes was observed (Api et al. 2019b).

In silico

No structural alerts for mutagenicity were present for any of the chemicals or its potential skin metabolites. Simulation of S9 metabolism indicated that some aldehyde metabolites of the chemical have a theoretical capacity to bind DNA (OECD QSAR Toolbox v4.2).

The knowledge based expert system DEREK Nexus version 6.0.1 was utilised to estimate the mutagenicity potential of the chemical. The chemicals and their metabolites did not match any structural alerts or examples for (bacterial in vitro) mutagenicity. Additionally, the chemical structure did not contain any unclassified or misclassified features and was; therefore, predicted negative for mutagenicity.

Carcinogenicity

No data are available for the chemicals in this group.

Reproductive and development toxicity

No data are available for the chemicals in this group.

Human health risk characterisation

Critical health effects

The critical health effect for risk characterisation is the local effect of skin sensitisation.

Public risk

Risk estimates related to use of cosmetic and personal care products

There is potentially widespread public exposure to methyl 2-octyonate and methyl 2-nonyoate, as the chemicals are present in various types of cosmetic products. The highest exposure to methyl 2-octyonate and methyl 2-nonyoate is expected to be from fine fragrances. No widespread public exposure is expected to the other chemicals in this group as they are prohibited in the IFRA Standard.

Although use in Australia is not known, methyl 2-octyonate and methyl 2-nonyoate are expected to be used as fragrance ingredients in personal care products. The use of chemicals in this group are expected to be controlled by members of IFRA through application of concentration limits in fragrance products. The highest concentrations of a fragrance is generally in fine fragrances (perfumes). The IFRA Standard limits the concentrations of methyl 2-octyonate and methyl 2-nonyoate in fine fragrances to 0.047% and 0.01%, respectively.

The acceptable exposure level (AEL) and AEC was calculated based on the EC3 for methyl 2-octynoate (0.45%) (see **Skin sensitisation section**). Although a higher EC3 value (2.5%) was determined for methyl 2-nonynoate, positive HRIPT results were observed at concentrations close to the EC3 value for methyl 2-octynoate (Table 3). Accordingly, the EC3 value for methyl 2-octyonate was also assigned to methyl 2-nonyoate. The quantitative risk assessment conducted by AICIS established an AEC of 0.01% (Table 4).

Table 3 Sensitisation data for methyl 2-octyonate and methyl 2-nonyoate

Chemical	LLNA EC3	HRIPT (NOAEL)	HRIPT (LOAEL)
Methyl 2-octyonate	0.45% (112 µg/ cm^2)	118 µg/cm^2 (n=104)	Not available
Methyl 2-nonyoate	2.5% (625 µg/ cm^2)	24 µg/cm^2 (n=100)	118 µg/cm^2 (6/138)

Table 4 Quantitative risk assessment for use of methyl 2-octynaote and methyl 2-nonynoate in fine fragrances

Chemical	WOE EC3 (%)	Amount applied (mL/day)	Overall safety factor	AEL (µg/cm^2/day)	Acceptable exposure concentration (%)
Methyl 2-octyonate	0.45	0.025	300	0.35	0.01
Methyl 2-nonyoate	0.45	0.025	300	0.35	0.01

The AEC (calculated by AICIS) for fine fragrances for the chemicals in this group (Table 4) is approximately 5 times lower than the concentration limit for methyl 2-octynoate in the IFRA Standard (0.047%) and has the same concentration limit set by IFRA for methyl 2-nonyoate (0.01%) (Table 1).

There are currently no restrictions on domestic and cosmetic uses of the chemical in Australia.

Given the identified health hazard of skin sensitisation, the evidence indicates that there is a risk to the public that requires management (see **Proposed means for managing any risks** section). The risk could be managed by including these chemicals in the Poisons Standard.

The risks of use of the chemicals in e-cigarettes and cigarettes have not been assessed due to the absence of relevant toxicity data (systemic toxicity, inhalation toxicity and respiratory sensitisation).

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