Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

# Tocopherols and their salts and esters

## Evaluation statement

**26 June 2023**

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# AICIS evaluation statement

## Subject of the evaluation

Tocopherols and their salts and esters

## Chemicals in this evaluation

| Name | CAS registry number |
|---|---|
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)- | 10191-41-0 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,8-dimethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- | 119-13-1 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- | 16698-35-4 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, [2R*(4R*,8R*)]-(.+-.)- | 2074-53-5 |
| 9,12-Octadecadienoic acid, (Z,Z)-, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, [2R*(4R*,8R*)]-(.+-.)- | 36148-84-2 |
| 3-Pyridinecarboxylic acid, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, [2R-[2R*(4R*,8R*)]]- | 43119-47-7 |
| Butanedioic acid, mono[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl] ester, [2R-[2R*(4R*,8R*)]]- | 4345-03-3 |
| 3-Pyridinecarboxylic acid, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, [2R*(4R*,8R*)]-(.+-.)- | 51898-34-1 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate, [2R*(4R*,8R*)]- | 52225-20-4 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- | 54-28-4 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate, [2R-[2R*(4R*,8R*)]]- | 58-95-7 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- | 59-02-9 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, dihydrogen phosphate, disodium salt, [2R*(4R*,8R*)]-(.+-.)- | 60934-46-5 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate | 7695-91-2 |
| Poly(oxy-1,2-ethanediyl), .alpha.-[4-[[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]-1,4-dioxobutyl]-.omega.-hydroxy-, [2R-[2R*(4R*,8R*)]]- | 9002-96-4 |
| 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, dihydrogen phosphate, disodium salt | 97304-02-4 |

# Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

# Parameters of evaluation

The chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory). These chemicals have been assessed as a group as they are structurally similar and have similar use patterns. Following absorption, the tocopherol esters are expected to be hydrolysed to their respective tocopherol isomer. Some of the chemicals included in this evaluation are isomers of tocopherol that are listed as separate chemicals on the Inventory. This evaluation is a human health risk assessment for all identified industrial uses of the chemicals including use in non-nicotine e-cigarette liquids (vaping products).

# Summary of evaluation

## Summary of introduction, use and end use

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

Based on international use information, these chemicals are expected to have widespread and repeated use as antioxidants and skin conditioning agents in consumer products including cosmetics, cleaning and washing agents, and air freshener products. Tocopherol and tocopherol acetate have the most widespread use in cosmetic products. There is reported use of α-tocopherol at up to 5.4% in leave-on cosmetics and α-tocopherol acetate at up to 36% (nail cuticle softeners).

Internationally, *dl*-α-tocopherol acetate has been detected in e-cigarette liquids. It has not been identified in commercially available e-cigarette liquids in Australia. The inclusion of *dl*-α-tocopherol acetate as an ingredient in e-cigarettes appears to be largely limited to illicit THC-containing e-cigarettes. However, its use in non-nicotine containing e-cigarettes (vaping products) in Australia, cannot be ruled out.

These chemicals have non-industrial uses in nutritional supplements and listed medicines.

## Human health

### Summary of health hazards

Tocopherols are lipid-soluble, phenolic antioxidants expected to be absorbed via the oral route and minimally via the dermal route. Tocopherols are endogenous in humans. The most abundant and biologically active isomer in human tissues is *d*-α-tocopherol. Tocopherol esters preserve the antioxidant activity of the otherwise unstable tocopherol, and upon being hydrolysed, release the free tocopherol isomer. Tocopherols are metabolised into tocopheryl hydroquinones and are most commonly conjugated with glucuronic acid before excretion.

Based on the available data, chemicals in this group are expected to have low acute oral toxicity (median lethal dose (LD50) >3000 mg/kg body weight (bw)) and low acute dermal toxicity (LD50 >3000 mg/kg bw).

Limited data are available on the inhalation toxicity of tocopherols. Tocopherol acetate (CAS No. 7695-91-2) has been linked to human clinical cases of e-cigarette or vaping use-associated lung injury (EVALI) internationally.

Based on the available data, these chemicals may be slightly irritating to the skin, and are not expected to be eye irritants.

Based on the available data, *dl*-α-tocopherols are potential skin sensitisers, with low to moderate potency in animal tests. Positive results were reported for *dl*-α-tocopherol in a local lymph node assay (LLNA) (EC3 of 7.3%) and a guinea pig maximisation assay (GPMT). However, human patch testing studies with *dl*-α-tocopherol and *dl*-α-tocopherol acetate were mostly negative. Rates of reactions were at most, 1.1% for *dl*-α-tocopherol (concentrations ≥20%), and 0.5% for *dl*-α-tocopherol acetate (undiluted). The majority of reactions were classed as weak.

The weight of evidence suggests plant-derived *d*-tocopherols are not expected to be skin sensitisers, based on negative in silico data, animal data, and human case studies. Impurities in synthetically produced tocopherols may explain the positive skin sensitisation data for *dl*-tocopherols as opposed to the plant-derived *d*-tocopherol isomers. This possibility does not exclude other explanations but limits the suitability of read-across from synthetic tocopherols to plant-derived tocopherols for the skin sensitisation hazard. In addition, it is not possible to classify synthetically produced tocopherol esters such as *dl*-α-tocopherol acetate based on available data.

Based on the available data, these chemicals are not expected to cause serious systemic health effects following repeated exposure. Haematological changes occurred in rats administered high doses of tocopherols (>500 mg/kg bw/day) including increased clotting time and propensity for haemorrhage. These effects were reversible upon vitamin K supplementation. In humans, generally large amounts of tocopherol (up to 800 mg daily) have not produced adverse effects on clotting or vitamin K status.

Based on the available data these chemicals are not expected to have genotoxic or carcinogenic potential. Tocopherols and esters were consistently negative in in vitro and in vivo genotoxicity assays. The only changes in tumour incidence that occurred in carcinogenicity studies were a reduction in incidence of mammary tumours in rats.

Based on the available animal data, these chemicals are not expected to cause reproductive or developmental toxicity. No effects on fertility or development were observed in available studies.

### Hazard classifications relevant to worker health and safety

In this group, *dl*-α-tocopherols (CAS No. 10191-41-0 and CAS No. 2074-53-5) 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. This does not consider classification of physical hazards and environmental hazards.

| Health hazards | Hazard category | Hazard statement |
|---|---|---|
| Skin sensitisation | Skin sens. 1B | H317: May cause an allergic skin reaction |

## Summary of health risk

### Public

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

- by direct application of these chemicals to the skin/hair/lips/oral cavity
- by direct skin contact during use of domestic products
- by incidental skin and eye contact with these chemicals during use of domestic products
- by inhaling aerosols.

The public may also be exposed to *dl*-α-tocopherol acetate by inhaling vapours and aerosols following use of non-nicotine liquids in e-cigarette devices.

There is a low incidence of cases of sensitisation to *dl*-α-tocopherol and *dl*-α-tocopherol acetate in humans, despite widespread use. In addition, positive human patch test results were observed in studies where participants were exposed to concentrations at relatively high concentrations (≥20%). Consequently, although *dl*-α-tocopherols were positive for skin sensitisation in animal studies, these chemicals are considered unlikely to pose a significant risk of skin sensitisation under the current use patterns. Therefore, use of *dl*-α-tocopherols in cosmetic and domestic products in Australia does not present any risks to the public that require management.

Based on animal data, human clinical data, and in silico predictions, other tocopherols in this group are not expected to present a risk to the public under current use patterns in cosmetic and domestic products.

Although not definitively identified, the public may potentially be exposed to *dl*-α-tocopherol acetate in non-nicotine e-cigarette liquids. Tocopherols have been assessed for food use and found to be 'generally recognised as safe', inhalation toxicity data is often not a core component of such assessments. Therefore, information on inhalational effects is lacking. Internationally the chemical has been linked with the development of lung injury and mortality. *dl*-α-Tocopherol acetate is currently risk managed for use in nicotine vaping products. No specific controls are currently available for use in non-nicotine vaping products. Overall, the chemical may pose a risk to the public that requires management (see **Proposed means for managing the risk**).

### 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic local effects, *dl*-α-tocopherols could pose a risk to workers, particularly when handled in high concentrations. Control measures to minimise dermal exposure are needed to manage the risk to workers (see **Proposed means for managing the risk**). Based on the hazard profile, the other tocopherols in this evaluation are unlikely to pose a risk to workers.

# Proposed means for managing risk

## Public Health

### Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling list *dl*-α-tocopherol acetate 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 the chemical, the entry prohibits its use in products intended to be inhaled (e.g. non-nicotine e-cigarette fluids).

Consideration should be given to the following:

- the chemical is strongly suspected of causing EVALI
- the chemical is a prohibited ingredient in nicotine vaping products (TGA 2021).

As *dl*-α-tocopherol acetate is a prohibited ingredient in nicotine-containing e-cigarettes in Australia (TGA 2021), the suggested SUSMP entry should align with this prohibition so that the chemical is effectively banned in all e-cigarettes (vaping products) in Australia.

## Workers

### Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the 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 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.

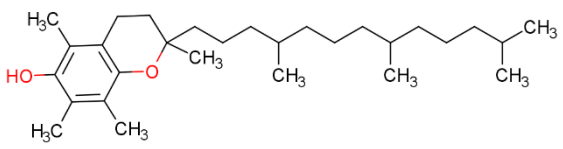
# Supporting information

## Grouping rationale

The chemicals in this group are tocopherols, and their salts and esters. Tocopherols belong to the group 'vitamin E' which comprises of 4 tocopherol and 4 tocotrienol isomers which all exhibit vitamin E activity. The 4 tocopherol isomers (α-, β-, γ- and δ-tocopherol) contain a common chromanol ring and phytyl chain, with differing methyl group substitution patterns on the chromanol ring. The phytyl chain contains 3 chiral centres. When cleaved, the tocopherol esters release their respective tocopherol isomer. These structurally related chemicals have been assessed as a group as they are expected to have similar uses, toxicity and bioavailability.

## Chemical identity

Tocopherols can be obtained from natural sources or derived synthetically. Production occurs in photosynthetic organisms with predominate sources including vegetable seeds and oils. Plant-derived tocopherols can be extracted and purified from such sources. Tocopherols have 3 stereocenters (*) which are all of the R configuration (d-form) when obtained from natural sources. Synthetic manufacture of tocopherols is also possible from isophytol and methylhydroquinones, producing racemic mixtures of stereoisomers (CIR 2002; EFSA 2015; Netscher 2007). Plant-derived and synthetic forms are often designated as *d-* or *dl-* tocopherols, respectively.

| | |
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)- |
| **CAS No.** | 10191-41-0 |
| **Synonyms** | *dl*-α-tocopherol<br>(±)-α-tocopherol<br>*all-rac*-α-tocopherol<br>3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-benzopyran-6-ol |
| **Molecular formula** | C29H50O2 |
| **Molecular weight (g/mol)** | 430.71 |
| **SMILES** | OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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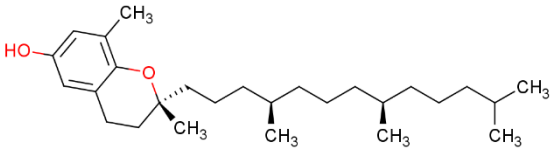
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,8-dimethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 119-13-1 |
| **Synonyms** | *d*-δ-tocopherol<br>(+)-δ-tocopherol<br>(R,R,R)-δ-tocopherol<br>E 309 |
| **Molecular formula** | C27H46O2 |
| **Molecular weight (g/mol)** | 402.65 |
| **SMILES** | OC=1C=C(C=2OC(C)(CCC2C1)CCCC(C)CCCC(C)CCCC(C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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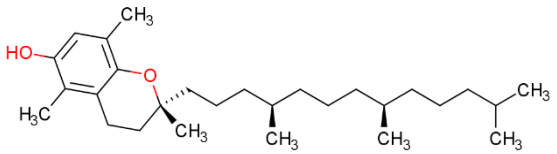
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 16698-35-4 |
| **Synonyms** | 2H-1-benzopyran-6-ol, 3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-, (+)-<br>*d*-β-tocopherol<br>(*R*,*R*,*R*)-β-tocopherol |
| **Molecular formula** | C28H48O2 |
| **Molecular weight (g/mol)** | 416.68 |
| **SMILES** | OC=1C=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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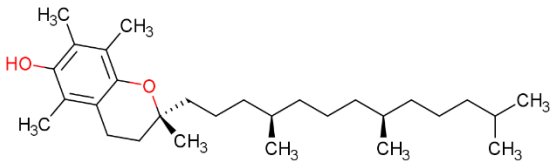
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, [2R*(4R*,8R*)]-(.+-.)- |
| **CAS No.** | 2074-53-5 |
| **Synonyms** | *dl*-α-tocopherol<br>(±)-2R,4′R,8′R-α-tocopherol |
| **Molecular formula** | C29H50O2 |
| **Molecular weight (g/mol)** | 430.71 |
| **SMILES** | OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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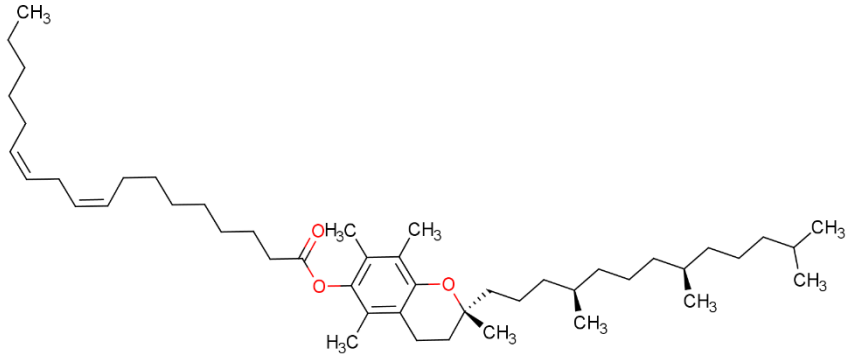
|---|---|
| **Chemical name** | 9,12-Octadecadienoic acid, (Z,Z)-, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, [2R*(4R*,8R*)]-(.+-.)- |
| **CAS No.** | 36148-84-2 |
| **Synonyms** | *dl*-.α.-tocopherol linoleate<br>(±)-α-tocopherol linoleate<br>tocopheryl linoleate |
| **Molecular formula** | C47H80O3 |
| **Molecular weight (g/mol)** | 693.14 |
| **SMILES** | O=C(OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C)CCCCCCCC=CCC=CCCCCC |
| **Chemical description** | - |
| **Structural formula:** |  |

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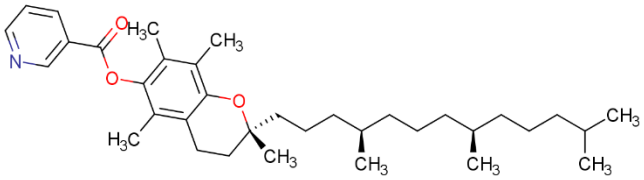
|---|---|
| **Chemical name** | 3-Pyridinecarboxylic acid, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 43119-47-7 |
| **Synonyms** | α-tocopherol nicotinate<br>tocopherol nicotinate |
| **Molecular formula** | C35H53NO3 |
| **Molecular weight (g/mol)** | 535.80 |
| **SMILES** | O=C(OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C=3C=NC=CC3 |
| **Chemical description** | - |

**Structural formula:**



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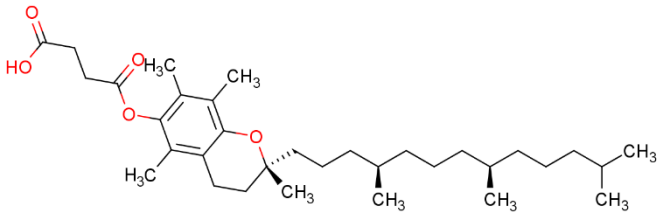
|---|---|
| **Chemical name** | Butanedioic acid, mono[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl] ester, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 4345-03-3 |
| **Synonyms** | α-tocopherol, succinate<br>(+)-α-tocopheryl succinate<br>*d*-α-tocopherol acid succinate |
| **Molecular formula** | C33H54O5 |
| **Molecular weight (g/mol)** | 530.78 |
| **SMILES** | O=C(O)CCC(=O)OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C |
| **Chemical description** | - |

**Structural formula:**



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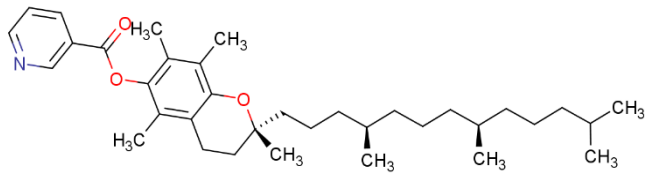
|---|---|
| **Chemical name** | 3-Pyridinecarboxylic acid, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl ester, [2R*(4R*,8R*)]-(.+-.)- |
| **CAS No.** | 51898-34-1 |
| **Synonyms** | α-tocopherol, nicotinate, (.+-.)-<br>*dl*-α-tocopheryl nicotinate<br>*rel*-(2R)-3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-2H-1-benzopyran-6-yl 3-pyridinecarboxylate |
| **Molecular formula** | C35H53NO3 |
| **Molecular weight (g/mol)** | 535.80 |
| **SMILES** | O=C(OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C=3C=NC=CC3 |
| **Chemical description** | - |
| **Structural formula:** |  |

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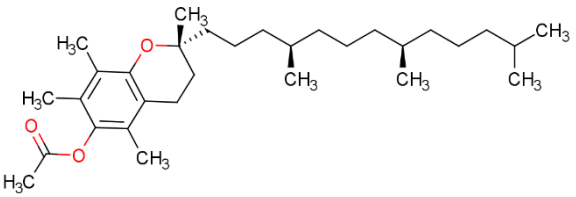
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate, [2R*(4R*,8R*)]- |
| **CAS No.** | 52225-20-4 |
| **Synonyms** | *dl*-.α.-tocopherol acetate<br>(±)-α-tocopherol acetate<br>*all-rac*-α-tocopheryl acetate<br>2H-1-benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, acetate, (2R)-rel- |
| **Molecular formula** | C31H52O3 |
| **Molecular weight (g/mol)** | 472.74 |
| **SMILES** | O=C(OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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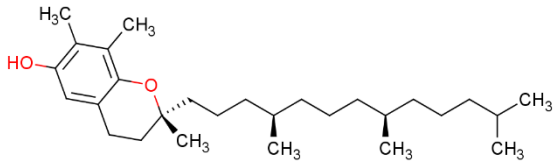
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 54-28-4 |
| **Synonyms** | *d*-γ-tocopherol<br>(+)-γ-tocopherol<br>(2R,4′R,8′R)-γ-tocopherol<br>6-chromanol, 2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-, (+)- |
| **Molecular formula** | C28H48O2 |
| **Molecular weight (g/mol)** | 416.68 |
| **SMILES** | OC=1C=C2C(OC(C)(CC2)CCCC(C)CCCC(C)CCCC(C)C)=C(C1C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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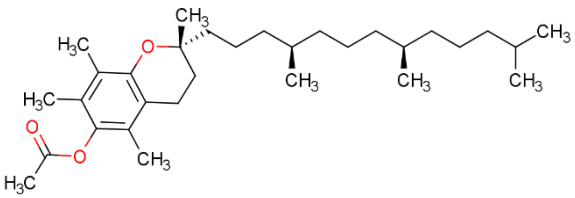
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 58-95-7 |
| **Synonyms** | α-tocopherol acetate<br>(+)-α-tocopherol acetate<br>*d*-α-tocopherol acetate<br>(R,R,R)-α-tocopheryl acetate |
| **Molecular formula** | C31H52O3 |
| **Molecular weight (g/mol)** | 472.74 |
| **SMILES** | O=C(OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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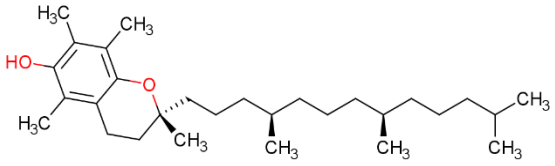
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 59-02-9 |
| **Synonyms** | (+)-α-tocopherol<br>*d*-α-tocopherol<br>(*all*-R)-α-tocopherol<br>RRR- α-tocopherol<br>E 307 |
| **Molecular formula** | C29H50O2 |
| **Molecular weight (g/mol)** | 430.71 |
| **SMILES** | OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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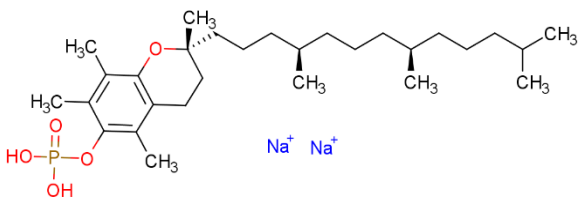
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, dihydrogen phosphate, disodium salt, [2R*(4R*,8R*)]-(.+-.)- |
| **CAS No.** | 60934-46-5 |
| **Synonyms** | α-tocopherol disodium phosphate<br>2*H*-1-benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-, dihydrogen phosphate, disodium salt, (2*R*)-*rel*- |
| **Molecular formula** | C29H51O5P.2Na |
| **Molecular weight (g/mol)** | 556.67 |
| **SMILES** | [Na].O=P(O)(O)OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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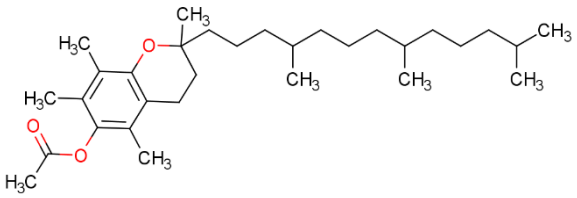
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate |
| **CAS No.** | 7695-91-2 |
| **Synonyms** | *dl*-.α.-tocopherol acetate<br>(±)-α-tocopherol acetate<br>*all-rac*-α-tocopherol acetate |
| **Molecular formula** | C31H52O3 |
| **Molecular weight (g/mol)** | 472.74 |
| **SMILES** | O=C(OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C)C |
| **Chemical description** | - |
| **Structural formula:** |  |

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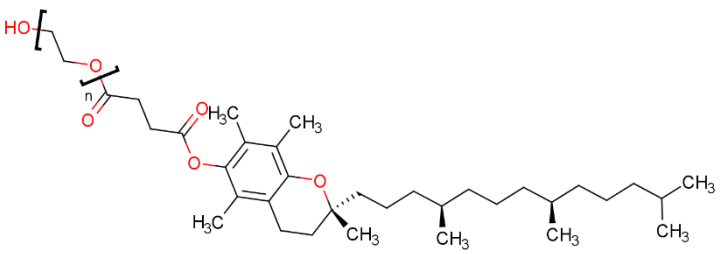
| **Chemical name** | Poly(oxy-1,2-ethanediyl), .alpha.-[4-[[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]-1,4-dioxobutyl]-.omega.-hydroxy-, [2R-[2R*(4R*,8R*)]]- |
| **CAS No.** | 9002-96-4 |
| **Synonyms** | tocofersolan<br>d-α-tocopheryl poly(ethylene glycol) 1000 succinate |
| **Molecular formula** | (C2H4O)nC33H54O5 |
| **Molecular weight (g/mol)** | Unspecified |
| **SMILES** | O=C(OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C)CCC(=O)OCCO |
| **Chemical description** | - |
| **Structural formula:** |  |

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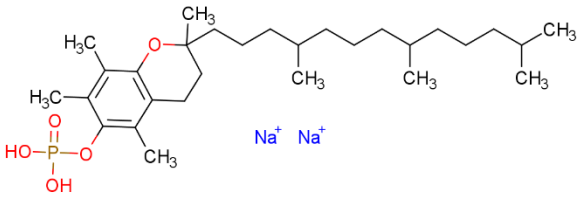
|---|---|
| **Chemical name** | 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, dihydrogen phosphate, disodium salt |
| **CAS No.** | 97304-02-4 |
| **Synonyms** | - |
| **Molecular formula** | C29H51O5P.2Na |
| **Molecular weight (g/mol)** | 556.67 |
| **SMILES** | [Na].O=P(O)(O)OC=1C(=C(C=2OC(C)(CCC2C1C)CCCC(C)CCCC(C)CCCC(C)C)C)C |
| **Chemical description** | - |

**Structural formula:**



# Relevant physical and chemical properties

Relevant physical and chemical properties for the group were obtained from CAS Scifinder$^{n}$, and the 2002 review on tocopherols published by the Cosmetic Ingredient Review Expert Panel (CIR 2002).

Tocopherols are generally viscous, oily liquids which may be pale yellow to reddish brown in colour. Some esters and salts may be waxy solids or powders. Melting points range from -(α-tocopherol acetate) to 75ºC (α-tocopherol succinate). Tocopherols readily oxidise upon exposure to air and light; however, prior to hydrolysis, tocopherol esters are often more resistant to oxidation compared to their parent tocopherol isomers. Boiling points of the group are high (>200ºC) and vapour pressures are low. With the exception of the tocopherol phosphates (CAS No. 60934-46-5; CAS No. 97304-02-4) and *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4), these chemicals are practically insoluble in water. Partition coefficients (Log $K_{OW}$) are generally high (>4.5).

# Introduction and use

## Australia

No specific Australian use, import, or manufacturing information has been identified for the chemicals in this group. However, the uses of these chemicals in Australia are unlikely to be significantly different to those uses identified internationally.

Non-industrial uses for this group include nutritional supplements and components of listed medicines (TGA 2022).

## International

The following international uses have been identified through the:

- European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers (REACHa n.d.; REACHb n.d.; REACHc n.d., REACHd n.d.; REACHe n.d.)
- Consumer Products Information Database (CPID) (DeLima Associates n.d.)
- Cosmetic Ingredient Review reports (CIR 2002; CIR 2018)
- International Fragrances Association (IFRA) transparency list (IFRA n.d.)

Most chemicals in this evaluation have reported use in personal care products and cosmetics, most commonly functioning as antioxidants and skin conditioning agents. Data from the United States of America (USA) indicated an increase in the reported use of tocopherol and tocopherol acetate in cosmetic products from 1998 to 2014 (CIR 2018). Reported maximum concentrations of tocopherols in cosmetic products included:

- leave-on products (5.4% α-tocopherol and 36% α-tocopherol acetate)
- rinse-off products (3% α-tocopherol and 25% α-tocopherol acetate)
- baby products including lotions, oils, and creams (1%)
- make-up preparations for application on or near the eye (4.9%)
- products that come into contact with mucous membranes (3%)
- aerosol and pump hair sprays (0.2% and 1%, respectively).

The highest reported use concentration of 36% for α-tocopherol acetate was in cuticle softening products, The compiled CIR use and concentration data relates to both plant derived and synthetically produced tocopherols. The majority of submissions to the Voluntary Cosmetic Registration Program survey were identified as generic tocopherol and tocopherol acetate. The Consumer Products Information Database (CPID) reported use concentrations for α-tocopherol acetate in cosmetic and personal care products such as shampoos at 0.1-1% and hair conditioners at <0.1% (DeLima Associates n.d.).

The following tocopherols in this group are listed on the International Fragrances Association (IFRA) transparency list, where they are likely to be used as antioxidants:

CAS No. 10191-41-0 (*dl*-α-tocopherol)
CAS No. 54-28-4 (*d*-γ-tocopherol)
CAS No. 59-02-9 (*d*-α-tocopherol)
CAS No. 60934-46-5 (α-tocopherol disodium phosphate)
CAS No. 7695-91-2 (*dl*-α-tocopherol acetate).

CAS No. 119-13-1 (*d*-δ-tocopherol) and CAS No. 7695-91-2 (*dl*-α-tocopherol acetate) have reported use in air freshener products.

CAS No. 119-13-1 (*d*-δ-tocopherol), CAS No. 59-02-9 (*d*-α-tocopherol) and CAS No. 7695-91-2 (*dl*-α-tocopherol acetate) have reported uses in surface cleaners, polishes and waxing products.

Internationally, *dl*-α-tocopherol acetate has been detected in illicit THC containing e-cigarette liquids, where it is added as a diluent (Krishnasamy et al. 2020). Concentrations were reported to range from 23–88% in samples obtained from vape users who developed EVALI in the USA (FDAa n.d.). In the illicit market, *dl*-α-tocopherol acetate is thought to be used primarily in THC-containing e-cigarette liquids due to its viscosity, which is similar to that of pure THC oil. In contrast, nicotine e-cigarette liquids have much lower viscosity and the addition of *dl*-α-tocopherol acetate is not favoured (Blount et al. 2020). The inclusion of *dl*-α-tocopherol acetate as an ingredient in e-cigarettes appears to be largely limited to 'bootleg' or 'at home' production of THC-containing e-cigarette liquids (Blount et al. 2020; Taylor et al. 2019). However, its use in both nicotine-containing and non-nicotine containing e-cigarettes (vaping products) in Australia, cannot be ruled out. Analysis of commercially available e-cigarette liquids in Australia so far has not detected this chemical (Larcombe et al. 2022).

No specific information is available for CAS No. 97304-02-4.

# Existing Australian regulatory controls

## AICIS

No specific controls are currently available for these chemicals.

## Public

The chemical *dl*-α-tocopherol acetate is listed in Schedule 1 of the *Therapeutic Goods (Standard for Nicotine Vaping Products) (TGO 110) Order 2021*. Schedule 1 substances must not be added as an ingredient to nicotine vaping products (TGA 2021).

### Workers

These chemicals are not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (SWA n.d.).

## International regulatory status

### Exposure standards

There are no specific exposure standards for the chemicals in this group.

### Canada

Although not specifically listed in the 'Industry Guide to Vaping Products Subject to the Canada Consumer Product Safety Act', *dl*-α-tocopherol acetate is expected to be covered. The guide stipulates that solvents known to be toxic to humans should never be added to vaping substances, and that substances with known inhalation risks should never be added to vaping substances (Government of Canada n.d.).

### United States of America

The Expert Panel for Cosmetic Ingredient Safety assessed the safety of tocopherols used in cosmetic formulations as antioxidants and emollients in 2002 and again in 2018. The panel concluded that the chemicals are safe in the present practices of use and concentration described in the safety assessments (CIR 2002; CIR 2018). The panel noted in the original 2002 report and the 2018 reassessment that skin irritation and sensitisation potential for these chemicals were not of concern.

Tocopherols are currently under the list of substances generally recognised as safe (GRAS) as food additives when used in accordance with the Good Manufacturing Practice (FDAb n.d.).

### United Kingdom

The chemicals in this group including *dl*-α-tocopherol acetate are not specifically listed in the 'Advice on ingredients in nicotine containing liquids in electronic cigarettes and refill containers' as substances not permitted as ingredients in e-cigarette liquids. However, they may be covered by the entry 'Vitamins used as food supplements' and prohibited from use for this reason. *dl*-α-Tocopherol acetate may also be covered and not permitted as ingredients in e-cigarette liquids as they may pose a risk to human health in heated or unheated form (UK MHRA n.d.).

## Health hazard information

### Toxicokinetics

Tocopherols are lipid soluble chemicals that rely on emulsification with dietary fats to form micelles that are absorbed across the gastrointestinal tract. Absorption of tocopherols is incomplete (varying between 20–80%), as efficiency can vary greatly between individuals and is influenced by factors such as the amount of dietary lipids ingested, amount of

tocopherol present and biliary function (Bjørneboe et al. 1990; SCF 2003). In both humans and rats, the proportion of absorbed tocopherol decreases as dosage increases (Kitagawa and Mino 1989; Traber et al.1986). Tocopherol esters are rapidly hydrolysed to release the respective tocopherol isomer. Gastrointestinal absorption does not differ greatly between free tocopherols and tocopherol esters (SCF 2003).

Intestinal absorption of tocopherols via the lymphatic pathway is the primary absorption route and relies on the presence of exogenous lipids (Bjørneboe et al. 1990). Absorption from the gut is selective, as hepatic tocopherol transport protein (α-TPP) targets α-tocopherol over other isomers such as β, γ and δ for which it has less affinity. This results in preferential selection of α-tocopherol by the liver (EFSA 2015). Synthetic tocopherol, which is an equal mixture of stereoisomers, has half the oral bioavailability of naturally derived tocopherol (*d*-α-tocopherol). Water-soluble *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) does not rely on bile or pancreatic enzymes for intestinal absorption and instead forms micelles that are absorbed via passive diffusion through cell membranes (EFSA 2007). The molecule enters cells unchanged before being enzymatically cleaved to release free α-tocopherol (EFSA 2007).

Following absorption, tocopherols are carried by lipoproteins into the systemic circulation where they can distribute to almost all body tissues with varying affinity, including the skin, brain, kidneys, liver and heart (CIR 2002). Among the tocopherol isomers, α-tocopherol has the most biological activity, and is the most abundant and retained form of tocopherol in animal and human tissues (EFSA 2015). The tissues reported to be most rich in α-tocopherol include the liver, skeletal muscle, adrenals, lungs, and adipose tissue (Bjørneboe et al. 1990). Analysis of human adipose tissue indicated that on average approximately 81% (61-811 µg/g) of total tocopherol was α-tocopherol, while other isomers like β, γ and δ represented smaller amounts, with δ-tocopherol only present at minimal amounts (Parker 1988). Plasma concentrations of tocopherol in healthy adults are approximately 1 mg/dL, and endogenous skin concentrations of tocopherol are approximately 1 nmol/g (CIR 2002).

Dermal absorption of free tocopherols and esters is estimated to be 5% for humans (REACHf n.d.), with penetration of mouse skin reported to be 3 times higher (CIR 2002). Absorption rates and conversion of esters to free tocopherol in the skin is influenced by formulation and delivery. In a neonatal rat model, penetration of *dl*-α-tocopherol acetate in commercial cosmetic products (concentrations from 0.12–1.53%) into the deep layers of skin varied from 10–12.5%. However, no free tocopherol arising from conversion of the ester was detected (Nada et al. 2011). In a similar study, penetration of radiolabelled tocopherol acetate was followed by conversion into free tocopherol in the skin of mice. Conversion rates ranged from 4.13–6.01% in the application site and the surrounding area (Trevithick and Mitton 1993). A cream formulation containing 125 mg/g tocopherol acetate applied twice daily to the forearms of 11 human participants for 3 months resulted in a substantial increase in the amount of tocopherol acetate in the skin. There were no changes to systemic levels of tocopherols (CIR 2002), suggesting minimal dermal absorption had occurred.

In humans, this class of chemicals are expected to be metabolised by hepatic oxidation into tocopheryl quinones. Tocopheryl quinones are converted to tocooheryl hydroquinones and finally conjugated for excretion, most commonly with glucuronic acid. The major route of elimination is via the biliary secretion system and faeces (Bjørneboe et al. 1990). Another form of metabolism in humans is the conversion of tocopherols into their respective carboxyethyl hydroxychromans. Excretion can occur via the urinary system as soluble glucuronide conjugates (Liu and Jiang 2020). If not absorbed in the gastrointestinal system, or if the antioxidant capacity is unused, the majority of tocopherols are excreted in the faeces via the biliary system (Liu and Jiang 2020).

## Acute toxicity

Based on the available data, the chemicals in this group have low acute oral toxicity.

The LD50 for chemicals in this group are reported to range from >3000 to >10000 mg/kg bw in rats. The most common sublethal signs of toxicity reported include transient diarrhoea occurring within 1–2 days of dosing.

In a non-GLP compliant acute oral toxicity study conducted similarly to the Organisation for Economic Co-operation and Development (OECD) TG 401, Wistar rats of both sexes (n = 10) were treated with a single dose of *dl*-α-tocopherol. The LD50 was >4000 mg/kg bw. Reported sublethal signs of toxicity included cyanosis and respiratory depression (REACHb n.d.).

In a non-GLP compliant acute oral toxicity study conducted similarly to OECD TG 401, Wistar rats of both sexes (n = 5) were treated with a single dose of tocopherol blend (CAS No. 1406-66-2). The median lethal dose was >7500 mg/kg bw. Reported sublethal signs of toxicity included diarrhoea on day 2 which lasted for 24 hours (REACHf n.d.).

In a non-GLP compliant acute oral toxicity study conducted similarly to OECD TG 401, Sprague Dawley (SD) rats of both sexes (n = 10) were treated with a single oral bolus dose of *dl*-α-tocopherol acetate (CAS No. 7695-91-2). The LD50 was determined to be >10,000 mg/kg bw. Reported sublethal signs of toxicity included slight diarrhoea and slight skin erythema on day one (REACHd n.d.).

In a non-GLP compliant acute oral toxicity study conducted similarly to OECD TG 401, mature CD rats of both sexes (n = 10) were treated with a dose of *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4). The median lethal dose was >7000 mg/kg bw. Reported sublethal signs of toxicity included transient lethargy and diarrhoea on day one (CIR 2002; Krasavage and Terhaar 1977).

In a non-guideline study, oral gavage of 2000 mg/kg bw *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) in male Beagle dogs (n = 2) resulted in diarrhoea one day after administration, with no other abnormal clinical signs noted (EFSA 2007).

### Dermal

Based on the limited data, the chemicals in this group have low acute dermal toxicity.

The dermal LD50 for *dl*-α-tocopherol in albino rats is reported as >3000 mg/kg bw. Reported signs of toxicity included mild skin changes such as erythema from 24–48 hours after administration, progressing to abrasion, and inflammation peaking from 48 hours, particularly in females. Reductions in body weights were observed mainly in females, no gross pathological abnormalities were noted (REACHb n.d.).

The dermal LD50 for *d*-α-tocopherol (CAS No. 59-02-9) in New Zealand White (NZW) rabbits (5/sex/dose) is reported as >5000 mg/kg bw. Reported signs of toxicity were noted in some animals, including weight loss, reduced appetite, decreased activity, nasal discharge, and diarrhoea. Death occurred in one animal on day 14 of observation (REACHc n.d.).

The dermal LD50 for α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) in Crl:CD (SD)BR rats (5/sex/dose) is reported as >2000 mg/kg bw. There were no reported signs of clinical toxicity. All animals survived to day 14 of observation (CIR 2002).

### Inhalation

Limited information is available on the inhalation toxicity of the chemicals in this group.

Rats exposed to a saturated atmosphere of tocopherol nicotinate for 8 hours at 20ºC resulted in no mortality. No further details were provided (CIR 2002).

While tocopherols are used in cosmetic formulations that have potential for inhalation such as pump or aerosol sprays, there is low potential for released particles to access the lower respiratory tract due to sizes exceeding 10 µM from these types of products (CIR 2002).

Inhalation of *dl*-α-tocopherol acetate in tetrahydrocannabinol (THC)-containing e-cigarette liquids inhaled via vaping and e-cigarette devices has been linked to EVALI (e-cigarette or vaping use-associated lung injury). From a period of July 2019 to February 2020 a significant increase in the incidence of EVALI occurred in the USA, resulting in 2807 hospitalisations and 68 deaths (Krishnasamy et al. 2020). The United States Centers for Disease Control and Prevention (CDC) reported that USA state health authorities strongly linked *dl*-α-tocopherol acetate in e-cigarette liquids to the increased incidence of EVALI. This was supported by laboratory data that detected *dl*-α-tocopherol acetate in the lung fluid of EVALI patients who reported e-cigarette use within the 90 days of symptom onset (Blount et al. 2020). However, the CDC noted that evidence is not sufficient to rule out the contribution of other chemicals of concern. Investigations into the mechanism of EVALI indicated that tocopherol acetate is converted to ketene (CAS No. 463-51-4), a known respiratory irritant (Strongin 2020). Another proposal for the mechanism behind EVALI is the disruption of alveolar surfactant by increasing the amounts of synthetic tocopherols in the lipid membranes of alveoli, rather than endogenous tocopherol (O'Callaghan et al. 2022).

## Corrosion/Irritation

### Skin irritation

Based on the available data, the chemicals in this group may be slightly irritating to skin. Hazard classification is not warranted.

In a GLP compliant irritation study conducted according to OECD TG 404 *dl*-α-tocopherol (CAS No.10191-41-0) (100%) was applied to the skin of 3 NZW rabbits under semi-occlusive conditions for 4 hours. Observations were recorded at 1, 24, 48 and 72 hours after patch removal, for 2 of the animals observations were also taken at 7 and 14 days. The following mean scores for individual animals were reported for observations at 24, 48 and 72 hours: 0, 2, and 0.33 for erythema and 0, 0.67 and 0.33 for oedema. The effects were reversible within 14 days (REACHb n.d.).

In a GLP compliant irritation study conducted according to OECD TG 404 *d*-α-tocopherol (CAS No. 59-02-9) (100%) was applied to the intact and abraded skin of 6 NZW rabbits under occlusive conditions for 24 hours. Observations were recorded at 24 and 72 hours post patch removal. The following mean scores for intact skin of individual animals were reported: 0.5, 1, 1, 1, 0.5 and 1 for erythema and 0, 0, 0.5, 0, 0 and 0 for oedema. For abraded skin, the following scores for individual animals were reported: 0.5, 1, 1, 1, 0.5 and 1 for erythema and 0, 0, 0.5, 0, 0 and 0 for oedema. Slight erythema occurred that was not fully

reversible at 72 hours. Very minor oedema was observed but was fully reversible at 72 hours (REACHc nd.). A study completed under similar conditions reported a mean primary irritation score of 1.17. In this study the skin was first abraded prior to chemical application and occlusive dressings were used. The duration of exposure was 4 and 24 hours (REACHc n.d.).

In a GLP compliant irritation study conducted according to OECD TG 404 *dl*-α-tocopherol acetate (CAS No. 7695-91-2) (100%) was applied to the skin of 3 White Vienna rabbits under semi-occlusive conditions for 4 hours. *dl*-α-Tocopherol acetate was non-irritating to rabbit skin with mean irritation score for erythema and oedema being zero (REACHd n.d.). This is consistent with 3 studies reported in the CIR review which also indicate that *dl*-α-tocopherol acetate is not irritating to skin (CIR 2018).

Application of 75% *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) to shaved skin of 5 female Hartley guinea pigs under occlusive conditions for 24 hours resulted in no irritation over a 14 day observation period. No further details were provided (CIR 2002). In a similar guinea pig study with repeated dosing 9 times over a period of 11 days, moderate erythema was observed in animals after 4 doses and 9 doses (number of animals and sex unspecified) (CIR 2002).

### Eye irritation

Based on the available data, the chemicals in this group have low potential for eye irritation.

In GLP compliant irritation studies conducted according to OECD TG 405, *dl*-α-tocopherol (CAS No. 10191-41-0) (100%) applied to the eyes of 3 NZW rabbits for 72 hours resulted in no irritation (REACHb n.d.; REACHc n.d.). In a modified Draize test *dl*-α-tocopherol instilled into the eyes of rabbits produced weak to moderate irritation (redness) which was reversible by day 7 (CIR 2002). *dl*-α-Tocopherol acetate was slightly irritating in a similar study, with slight redness occurring from 1–48 hours post treatment that was reversible by 72 hours (CIR 2002; REACHd n.d.).

In an ocular irritation study, 0.1mL of 75% *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) was instilled into the 1 eye each of 6 NZW rabbits (sex unspecified). The eyes of 3 animals were rinsed and observed at 1 hour. Slight erythema of the conjunctivae was observed for all animals. In the unrinsed group, 1 animal displayed moderate erythema and 1 animal had slight erythema of the eyelid. No further details were provided (CIR 2002).

Read-across data for the structurally similar chemical *dl*-α-tocopherol nicotinate (CAS No. 86362-36-9) is available. The eye irritation potential of the chemical was determined using a reconstructed Human EpiOcular™ Cornea-like Epithelial Model (OECD TG 492). The relative mean tissue viability was 102.8%, as compared to the negative control. Under the conditions of this study and according to the test guideline, the chemical was not considered to be irritating to the eye (REACHg n.d.).

## Sensitisation

### Skin sensitisation

Based on the available data, *dl*-α-tocopherols (CAS No. 10191-41-0 and CAS No. 2074-53-5) of this group are potential skin sensitisers, with low to moderate potency in animals, warranting hazard classification.

However, human patch testing studies with *dl*-α-tocopherol and *dl*-α-tocopherol acetate were mostly negative. Rates of reactions were at most 1.1% for *dl*-α-tocopherol (concentrations ≥20%), and 0.5% for *dl*-α-tocopherol acetate (undiluted). The majority of reactions were classed as weak.

The weight of evidence suggests plant-derived *d*-tocopherols are not expected to be skin sensitisers, based on negative in silico data, animal data, and human case studies.

**Animal data**

In a local lymph node assay (LLNA) conducted in accordance with OECD TG 429, 4 female CBA mice received topical applications of *dl*-α-tocopherol (CAS No.10191-41-0) at 0.3, 1, 3, 10 or 30%, in ethanol. The reported stimulation indices (SI) were 0.61, 0.84, 1.1, 4.16 and 6.73 for concentrations of 0.3, 1, 3, 10 and 30% respectively. A threefold increase in lymphocyte proliferation (EC3) of 7.3% was reported (CIR 2018; REACHb n.d.).

In a GPMT conducted according to OECD TG 406, intradermal induction was performed on 20 female Dunkin-Hartley guinea pigs using 0.2% *dl*-α-tocopherol (CAS No. 2074-53-5) in light liquid paraffin. Occlusive topical induction was performed with *dl*-α-tocopherol at 25% in ethanol. The animals were challenged with an occlusive patch of 12.5% *dl*-α-tocopherol in ethanol. After challenge, reactions were reported in 37% of the animals. (CIR 2018; REACHb n.d.).

In an open epicutaneous test, *dl*-α-tocopherol (CAS No. 10191-41-0) at 3, 10, 30 or 50% in ethanol was applied to guinea pigs (3/sex/dose) 5 times per week for 4 weeks. The animals were challenged with the chemical at 1, 3, 5, or 10%, in ethanol. After challenge, skin sensitisation reactions were reported in animals challenged at doses >3%, but not those treated at lower concentrations (<1%) (REACHb n.d.).

In a GPMT conducted similarly to OECD TG 406, initial intradermal induction was performed on 20 female guinea pigs using *d*-α-tocopherol (CAS No. 59-02-9) at 0.5% in soybean oil. Topical induction was performed with the chemical at 5%, applied epidermally under occlusive conditions (in petroleum jelly). The animals were challenged with *d*-α-tocopherol at 1% in petroleum jelly. No skin reactions were observed in any animals after challenge (REACHc n.d.).

In a non-GLP compliant in vivo skin sensitisation study similar to OECD TG 406 (Buehler test), 5 Hartley guinea pigs (both sexes) were induced with 75% *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) (vehicle unspecified). The animals were challenged with 0.5mL of the chemical. None of the treated animals showed skin reactions. The chemical was reported to be non-sensitising in this study. No further details were provided (CIR 2002).

In a LLNA conducted in accordance with OECD TG 429, 5 female CBA/J mice received topical applications of mixed tocopherols at 1.13, 2.26 or 5.65 mg/mL in an aqueous gel formulation in water. The reported SI were 0.8, 0.7, and 1.8 for concentrations of 1.13, 2.26, and 5.65 mg/mL, respectively. Mixed tocopherols were considered non-sensitising in this study (CIR 2018; Libinaki et al. 2006).

In a photo allergenicity test, *dl*-α-tocopherol acetate (CAS No. 7695-91-2) did not elicit a photoallergenic response in guinea pigs (REACHd n.d.).

**In silico**

Modelling based on the mechanistic profiling functionality of the OECD quantitative structure-activity relationship (QSAR) Application Toolbox (OECD QSAR Toolbox v4.2) produced no structural alerts for *dl*-α-tocopherol (CAS No. 10191-41-0) or other tocopherol isomers, or their metabolites (skin metabolism and autoxidation) (OECD 2018). Acetate, succinate and lineolate tocopherol esters had structural alerts for protein binding.

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 2.4 was used to estimate the skin sensitisation potential of the chemicals in this group. The chemicals did not produce any structural alerts or examples for skin sensitisation and had no misclassified or unclassified features. Therefore, the chemicals were predicted to be non-sensitising (Llhasa Limited n.d.).

Skin sensitisation was investigated using OASIS-TIMES (tissue metabolism simulator) software (version 2.28.1). The chemicals in this group and their metabolites were predicted to be non-sensitising (OASIS LMC n.d.).

### Respiratory sensitisation

No data are available to evaluate respiratory sensitisation.

### Observation in humans

Several human repeat insult patch tests (HRIPT) have been conducted on *dl*-α-tocopherol and *dl*-α-tocopherol acetate both in cosmetic formulations and undiluted preparations. Many studies indicated no sensitisation potential, while a few reports showed positive reactions in participants. Rates of reactions were at most, 1.1% for *dl*-α-tocopherol (concentrations ≥20%), and 0.5% for *dl*-α-tocopherol acetate (undiluted). The majority of reactions were classed as weak. In addition, positive reactions were only seen in studies conducted in dermatology patients (conditions included allergic contact dermatitis, atopic dermatitis, eczematous dermatitis, or otherwise undisclosed) and not in healthy volunteer populations (see Table 1 and Table 2) (CIR 2002; Warshaw et al. 2021). There were positive patch tests for tocopherol lineolate in a particular cosmetic line distributed in Switzerland in 1992. However, the positive reactions were thought to be due to contamination from industrially produced tocopherol lineolate or its oxidation products (Perrenoud et al. 1994).

**Table 1. Summary of Human Repeat Insult Patch Tests conducted with dl-α-tocopherol.**

| Concentration | Number tested | Positive subjects (%) |
|---|---|---|
| 5% | 113 | 0% |
| 5% | 4887* | 0.2% |
| 20% | 97* | 1.03% |
| Unknown | 116* | 0.86% |
| Unknown | 1136* | 0.53% |
| Unknown | 1814* | 0.66% |
| 100% | 5090* | 1.1% |
| 100% | Unspecified* | 0.8% |

*study conducted in dermatology patients

**Table 2. Summary of Human Repeat Insult Patch Tests conducted with dl-α-tocopherol acetate.**

| Concentration | Number tested | Positive subjects (%) |
|---|---|---|
| 0.1% | 110 | 0% |
| 100% | 203 | 0% |
| 100% | 5000* | 0.5% |

*study conducted in dermatology patients

In a clinical maximisation study, tocopherol nicotinate tested at 10% in paraffin oil was not sensitising or irritating (no further details provided) (CIR 2002).

In 1992, a new line of cosmetic products (primarily body lotion, oil, and night cream) containing tocopherol lineolate was introduced to Switzerland and resulted in approximately 900 cases of contact dermatitis. Patch testing of the products (containing 1% tocopherol lineolate) in patients resulted in positive reactions ranging from 21–64%, with night cream producing the most positive reactions. Increasing the concentration of tocopherol lineolate from 1% to 2% and 10% did not increase the rate of positive reactions. Six patients were tested with undiluted tocopherol lineolate that had been artificially aged, and all 6 had positive or doubtful reactions. The authors of the study suggested that contamination of synthetically manufactured tocopherol lineolate, or an oxidised metabolite may act as a hapten to induce sensitisation. It was also noted that historical patch test data suggests synthetically-prodcued *dl*-tocopherols and not plant-derived *d*-tocopherols are more likely to be involved in cases of contact dermatitis (Perrenoud et al. 1994).

Synthetic tocopherols are likely to include impurities due to presence of reaction by-products. Identified impurities (EFSA 2015) include:

- *all-rac-trans*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-ol,
- *all-rac-cis*-2,3,4,6,7-pentamethyl-2-(4,8,12-trimethyltridecyl)-2,3-dihydrobenzofuran-5-ol
- 4-methoxy-2,3,6-trimethyl-5-[(all-*RS*,*E*)-3,7,11,15-tetramethylhexadec-2-enyl]phenol
- (all-*RS*,all-*E*)-2,6,10,14,19,23,27,31-octamethyldotriaconta-12,14,18-triene.

Information on the sensitisation potential of these impurities was not identified.

A number of clinical case reports have been summarised in reviews by the Cosmetic Ingredient Review Panel (CIR 2002; CIR 2018). Dermatitis associated with α-tocopherol in cosmetic products including oils, creams, and deodorants was reported in 15 cases with the majority presenting with positive patch testing to α-tocopherol. Dermatitis associated with α-tocopherol acetate was reported in 11 cases from products including “pure vitamin E oil”, creams and lipogels, with subsequent patch testing resulting in positive reactions to α-tocopherol acetate.

Patch testing conducted on 50 year old life long sufferer of atopic dermatitis diagnosed in childhood revealed sensitisation reactions to allergens in products frequently used by the patient. Following avoidance of the allergens, clearance of the dermatitis occurred and there were no additional exacerbations. Such cases indicate that sensitisation reactions relating to cosmetic ingredients can be difficult to distinguish from atopic dermatitis (Semaan et al. 2020).

## Repeat dose toxicity

### Oral

Based on the available data, chemicals in this group are not expected to cause serious systemic health effects following repeated oral exposure.

A large number of sub-chronic and chronic studies have been undertaken. In both a 13 week and a 16 month oral toxicity study, the no observed adverse effect level (NOAEL) was 125 mg/kg bw/day based on prolonged coagulation time at 500 mg/kg bw/day. This effect is believed to be due to the ability of tocopherols to inhibit or reduce the intestinal uptake of vitamin K (EFSA 2015).

In a 90 day study conducted similarly to OECD TG 408, Fischer 433 rats (10/sex/dose) were administered *d*-α-tocopherol acetate (CAS No. 58-95-7) by gavage at 125, 500, or 2000 mg/kg bw/day in corn oil daily for 90 days. Mortality in male rats receiving the highest dose was attributed to internal haemorrhage. Signs of toxicity in this dose group included diarrhoea, tachypnoea, nose bleeds, dark faeces and red crusts around the eyes. There were no adverse effects on body weight or food consumption. Relative liver weights were increased in females receiving ≥500 mg/kg bw/day. There was a significant dose related trend for changes in clotting and blood chemistry. This included prolongation of prothrombin and activated partial thromboplastin times, increases in reticulocytes, white blood cells and lymphocytes in males. In addition, activated partial thromboplastin time was also increased in males in the 500 mg/kg bw/day dose group. All rats treated with tocopherol acetate experienced interstitial inflammation and adenomatous hyperplasia of the lungs that was dose dependent. Changes included increased cellular proliferation in the presence of lipid laden ‘foamy’ macrophages. These effects were attributed to aspiration of tocopherol acetate during administration rather than systemic toxicity. Foamy macrophages are consistently present in the lungs of EVALI patients (Guerrini et al. 2020) (see **Acute toxicity – Inhalation**). The NOAEL for this study was determined to be 125 mg/kg bw/day by the Scientific Committee on Food based on the increased liver weights and changes in blood clotting parameters at 500 mg/kg bw/day (Abdo et al. 1986; EFSA 2015).

In a non-GLP 90 day oral repeat dose toxicity study (test guideline unspecified), CD weanling rats (30/sex/dose) were fed diets containing *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) equivalent to tocopherol doses of 0, 0.5, 50, or 500 mg/kg bw/day. No deaths, clinical signs of toxicity, or changes to food consumption and body

weights were observed. Blood and clinical chemistry showed no adverse findings. Histopathology of 15 rats/sex from each dose group showed no abnormal findings. There were no clotting effects noted such as excessive bleeding; however, haematological parameters such as prothrombin time were not measured. The remaining 15 rats/sex/dose were used for a reproductive toxicity study, which had no adverse findings (see **Reproductive and development toxicity**). An NOAEL of ≥500 mg/kg bw/day tocopherol was derived by the European Food Safety Authority Panel on Food Additives and Nutrient Sources (EFSA) on review (EFSA 2015; Krasavage and Terhaar 1977).

In a 5 day toxicity study, *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) was administered to male SD rats (n = 5) by gavage at doses of 500, 1000 or 2000 mg /kg bw/day. No clinical signs of toxicity were observed and there were no changes to haematological or clinical chemistry parameters (CIR 2018; Gopinathan et al. 2013).

In a 52 week chronic toxicity study (test guideline unspecified), rats (25/sex/dose) were administered *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) by gavage at 0, 100, 300 and 1000 mg/kg bw/day in deionised water. There were no changes to any clinical parameters and no treatment related deaths occurred. The NOAEL of this study was determined to be 1000 mg/kg bw day (EFSA 2007). These results were consistent with a similar study using dogs (4/sex/dose) administered the same dose levels (EFSA 2007).

**dl-α-Tocopherol acetate and d-α-tocopherol acetate**

The EFSA evaluated 6 additional oral repeat dose studies in rats with *dl*-α-tocopherol acetate or *d*-α-tocopherol acetate, these unpublished reports were submitted to EFSA for review (EFSA 2015; Gelbke et al. 1983; Pfister et al. 1999a; Pfister et al. 1999b; Pfister et al. 1999c; Pfister et al. 1999d; Wolz et al. 2000). Dosing across studies ranged from 180–2400 mg/kg bw/day most commonly with soybean oil used as a vehicle. Three studies were for a duration of 28 days, and 3 for 90 days. No deaths, clinical signs of toxicity, or changes in food consumption or body weights were observed over the course of any of the studies. Reversible increases in liver weights occurred in several studies, but this was considered an adaptive physiological response and not attributed to toxicity. Reductions in total lipids, total cholesterol and phospholipids were common to female rats treated with tocopherols. Prolonged prothrombin time and activated partial thromboplastin time occurred commonly in higher dose groups, affecting males more often than females and was attributed to the effects of tocopherol supplementation on vitamin K absorption. The EFSA panel determined NOAELs for these studies ranging from 600 to ≥2400 mg/kg bw/day and noted coagulation effects were common in studies of tocopherols (EFSA 2015). An additional study in hamsters dosed with 2000 mg/kg bw/day for 28 days showed similar results, with significantly increased prothrombin time and activated partial thromboplastin time in both males and females along with decreased total lipids, cholesterol, and phospholipids in females. In addition, females had increased alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and γ-glutamyltransferase activity (Pfister 1999e).

**dl-γ-Tocopherol**

In a GLP compliant 13 week oral repeat dose toxicity study conducted similarly to OECD TG 408 (with limitations such as less extensive histopathology), Wistar rats (6/sex/dose) were treated with *dl*-γ-tocopherol at doses of 800 or 1600 mg/kg bw/day by gavage in soybean oil. No mortality or clinical signs of toxicity occurred. There was a statistically significant and dose related decrease in platelet count, as well as reduced total lipids, total cholesterol and phospholipids. Bilirubin, alanine aminotransferase, and liver and spleen weights were elevated. Macrophage aggregates with fine cytoplasmic vacuoles in mesenteric lymph nodes were observed. No NOAEL was determined for this study (Pfister et

al. 1999d). A similar study by the same authors conducted with female hamsters administered 800 mg/kg bw/day for 13 weeks showed prolonged activated partial thromboplastin and prothrombin times, along with Increased bilirubin, alkaline phosphatase, and gamma-glutamyltransferase activities (Pfister et al 1999d). These results are consistent with another hamster study that used a 2000 mg/kg bw/day dosage (Pfister et al. 1999e).

**Mixed to copherol phosphates**

In a 90day GLP compliant study conducted according to OECD TG 408, SD rats (10/sex/dose) were treated with mixed tocopherol in their feed at approximately 0, 600, 1900 or 3200 mg/kg bw/day. Mixed tocopherols were reported to comprise of *d*-α-tocopherol phosphate and *d*-α-di-tocopherol phosphate (72% of the mixture), and *d*-a-tocopherol (17% of the mixture) in addition to water and phosphonic acid. The major expected metabolite of mixed tocopherols is α-tocopherol. No deaths, clinical signs of toxicity or changes in food intake were observed and no statistically significant or dose dependant body weight changes occurred. Statistically significant changes in clinical chemistry and haematology were not dose dependant and not consistent across animals in the same dose group. Blood clotting parameters were not tested. In high dose groups, histopathological examination revealed foreign material in the mesenteric lymph nodes and small intestine, thought to be tocopherol phosphate. An NOEAL of approximately 600 mg/kg bw/day was reported based on lymph node changes in the 2 highest dose groups (EFSA 2015; Gianello et al. 2007).

### Observation in humans

In humans generally large amounts of tocopherol (up to 800 mg daily) have not produced adverse effects on clotting or vitamin K status (SCF 2003).

Tocopherol concentrations in plasma have been shown to impact platelet function, increasing platelet aggregation under conditions of tocopherol deficiency, and inhibiting platelet aggregation when present at high levels in a concentration dependant manner in vitro (Bakaltcheva et al. 2009; Stuart and Oski 1979). However, a number of studies on supplementation of up to 800 mg/day α-tocopherol equivalent in healthy humans have shown no changes in platelet aggregation (SCF 2003). There is evidence that tocopherol supplementation in individuals with impaired vitamin K status may exacerbate already elevated prothrombin time and reduced clotting, including individuals on anticoagulant therapeutics such as long term warfarin therapy, or those with vitamin K deficiency (EFSA 2015; SCF 2003).

## Genotoxicity

Based on the available data, the chemicals in this group are not considered to be genotoxic. In vitro and in vivo studies were consistently negative.

### In vitro

Negative results were reported in the following in vitro genotoxicity studies:

**Tocopherol acetate**

Negative results for *dl*-α-tocopherol acetate were reported in 2 bacterial reverse mutation assays (OECD TG 471) in *Salmonella typhimurium* strains TA1535, TA97, TA98, TA100, TA1537, and TA102 with and without metabolic activation at concentrations up to 5000 µg/plate (REACHb n.d.).

Negative results were reported in an in vitro mammalian chromosome aberration assay (OECD TG 473) for *dl*-α-tocopherol acetate in human lymphocytes with and without metabolic activation at concentrations up to 1800 µg/plate (REACHb n.d.).

**Tocopherol isomers**

Negative results were reported in a chromosome aberration test with *dl*-α-tocopherol in Chinese hamster lung fibroblasts (CHL) without metabolic activation at concentrations up to 5000 µg/mL (REACHb n.d.).

Negative results were reported for an in vitro mammalian gene mutation assay in Chinese Hamster Ovary cells (CHO) with *d*-γ-tocopherol without metabolic activation at concentrations up to 14.6 µg/mL (34 µM) (Cornwell 2002; REACHd n.d.).

**Tocopherol succinate**

Weakly positive results were reported in a sister chromatid exchange (SEC) assay (OECD TG 479) with tocopherol succinate in CHO cells with metabolic activation 30–1000 µg/mL, but not without metabolic activation in concentrations from 5–30.2 µg/mL (CIR 2002). Negative results were reported in a chromosome aberration test in CHL cells with and without metabolic activation at concentrations up to 6000 µg/mL and 75 µg/mL tocopherol succinate respectively (CIR 2002).

**Tocopherol poly(ethylene glycol) 1000 succinate**

Negative results were reported in bacterial reverse mutation assays (OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2 uvrA, with and without metabolic activation at concentrations up to 5000 µg/plate in 2 independent studies (EFSA 2007).

Negative results were reported in a chromosome aberration test in CHL without metabolic activation at concentrations up to 200, 80 or 60 µg/mL for 6, 24 and 48 hours, respectively (EFSA 2007).

Negative results were reported in a chromosome aberration test in CHL with metabolic activation at concentrations up to 1600 µg/mL at 6 hours of incubation (EFSA 2007).

**Tocopherol phosphates**

Data are not available for the 2 phosphate tocopherols in this group; however, studies on mixed tocopherol phosphates showed negative results for genotoxicity (REACHf):

Negative results were reported in bacterial reverse mutation assays (OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 uvrA, with and without metabolic activation at concentrations up to 2825 µg/plate of mixed tocopherol phosphate.

Negative results were reported in 2 chromosome aberration tests in CHO cells with and without metabolic activation at concentrations up to 40.8 µg/plate and 67.8 µg/plate respectively.

### In vivo

Negative results were reported in the following in vivo genotoxicity studies.

In a mammalian erythrocyte micronucleus test conducted according to OECD TG 474, ICR mice (13/male/dose) were treated with α-tocopherol continuously in their diet at doses of 6 or 200 mg/kg bw/day for up to 50 weeks. The incidence of micronuclei formation in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity. Higher lipid peroxidation was observed in the bone marrow of groups treated with lower doses of the chemical, while lipid peroxidation was not reduced in the high dose group (CIR 2002).

In a mammalian erythrocyte micronucleus test rats (sex and number unspecified) were treated with *d*-α-tocopherol poly(ethylene glycol) 1000 succinate via gavage at single doses up to 2000 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes 24 hours after treatment did not increase in any of the treated groups, indicating a lack of clastogenicity (EFSA 2007).

## Carcinogenicity

Based on the available data the chemicals in this group are not considered to be carcinogenic following oral exposure.

In a 1983 combined chronic toxicity and carcinogenicity study conducted similar to OECD TG 453, 60 male and female SD rats received *dl*-α-tocopherol acetate in the diet at 500, 1000, or 2000 mg/kg bw/day for 104 weeks. No carcinogenic effects were noted. Histopathological examination at 52 weeks and 104 weeks noted no treatment related pathology or significant changes in organ weights. However, microscopic examination of the liver revealed non-dose dependent lipid-staining ‘foamy’ macrophages with the highest incidence in females (77% of treated females compared to 17% treated males). This effect was not observed in the control groups. Impaired haemostasis and haemorrhage in males in the 1000 and 2000 mg/kg bw/day groups were noted, with mortality occurring for 5 males in these groups. Increased prothrombin times were observed for the first 14 weeks in all male treatment groups. This, and the haemorrhagic incidents were alleviated upon supplementation with vitamin K, which continued to be administered via drinking water to all groups for the remainder of the study. No other haematological abnormalities were noted. A minor dose dependent reduction in the incidence of mammary fibroadenomas was observed in both sexes (Wheldon et al. 1983).

Modulation of carcinogenicity by tocopherols has been studied extensively in vivo, with the majority of results indicating either no effect on tumorigenesis or protective effects (CIR 2018).

## Reproductive and development toxicity

Based on the available data, the chemicals in this group are not expected to cause specific adverse effects on fertility, sexual function, or development following oral exposure. Reproductive and developmental toxicity studies on tocopherols have been extensively reviewed by the European Food Safety Authority, reporting consistent negative results (EFSA 2007; EFSA 2015).

In a non-GLP one generation reproductive toxicity study conducted similarly to OECD TG 415, rats (15/sex/dose) were administered *d*-α-tocopherol poly(ethylene glycol) 1000 succinate (CAS No. 9002-96-4) in their feed daily at 0.5, 50 or 500 mg/kg bw/day vitamin E equivalent. Across 2 groups, exposure started 112 and 175 days prior to mating for both sexes and continued for a total of 264–268 days. F1 generation pups were weaned at 21 days, and necropsy was performed on 4 pups from each litter 5 weeks after weaning. No adverse findings were observed across the F0 or F1 generations, including on fertility of male and female rats or foetal development. The reproductive NOAEL for this study was reported as >500 mg/kg bw day vitamin E (EFSA 2015; Krasavage and Terhaar 1977).

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