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

Heptanoic acid, 1,1′,1″-(1,2,3-propanetriyl) ester

Assessment statement (CA09905)

4 April 2025

Table of contents

AICIS assessment (CA9905)

Chemical in this assessment

Name	CAS registry number
Heptanoic acid, 1,1′,1″-(1,2,3-propanetriyl) ester	620-67-7

Reason for the assessment

An application for an assessment certificate under section 31 of the *Industrial Chemicals Act 2019* (the Act)

Certificate application type

AICIS received the application in a Health Focus type.

Defined scope of assessment

The chemical has been assessed:

- as imported into Australia at up to 10 tonnes/year
- as imported in neat form for reformulation into personal care products at up to 33% concentration
- as imported as a component in personal care products at up to 33% concentration

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia. It will be imported either in neat form for reformulation or in personal care products at up to 33% concentration.

The personal care products containing the assessed chemical will be used by professional workers and members of the general public.

Human health

Summary of health hazards

The assessed chemical belongs to the chemical group of triglycerides (Fiume et al 2022). The provided data (see **Supporting information**) indicate that the chemical is:

- of low acute oral and dermal toxicity
- irritating to the skin
- not irritating to eyes
- not a skin sensitiser

- not considered to be genotoxic

The assessed chemical is not likely to cause systemic toxicity following repeated or prolonged exposure. The No Observed Adverse Effect Level (NOAEL) in rats was estimated to be > 2,304 mg/kg bw/day in a 9-month feeding study with the assessed chemical dosed at 64% concentration.

Information from 2 *in vivo* rabbit skin irritation studies (OECD TG 404) and 1 *in vitro* Reconstructed Human EpiDermis (RHE) Test (OECD TG 439) was provided. In one *in vivo* study severe skin erythema and oedema with brown discolorations, dryness, sanguineous lacerations, severe extensive subcutaneous haemorrhage were observed in test animals up to 72 hours after an exposure to undiluted assessed chemical. Scaling was also observed in test animals after 6 days from the exposure. However, the recent *in vitro* RHE study indicated no irritation according to the OECD TG 439 criteria. Based on the weight of evidence, the assessed chemical is considered irritating to the skin but not meeting the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) criteria for classification.

No inhalation toxicity data were submitted on the assessed chemical.

Hazard classifications relevant for worker health and safety

Based on the data provided by the applicant, the assessed chemical does not satisfy the criteria for classification according to the GHS (UNECE 2017) for hazard classes relevant for worker health and safety as adopted for industrial chemicals in Australia.

Summary of health risk

Public

The public will be widely and repeatedly exposed to the assessed chemical at concentrations of up to 33% through the use of various personal care products. The principal route of exposure will be dermal, while incidental oral, ocular or inhalation exposure is also possible.

Inhalation exposure may occur particularly when the personal care products containing the assessed chemical are applied by spray. Fiume et al (2022) noted that, in spray products, inhalable droplets/particles would be mostly deposited in the nasopharyngeal or bronchial regions of the respiratory tract and would not be respirable to an appreciable amount. If inhaled, the droplets/particles would not present toxicological concerns based on the chemical and biological properties of triglycerides evaluated.

The assessed chemical is irritating to the skin at 100% concentration (neat), but it does not meet the GHS criteria for hazard classification. It is expected that once the chemical is reformulated into the personal care products, the skin irritation effects will be further reduced, requiring no risk control measures for the public.

No quantitative risk assessment for repeated exposure of the public was conducted for the assessed chemical as the NOAEL for repeated dose oral toxicity was > 2,000 mg/kg bw/day in rats as established in the 9-month feeding study (see **Supporting information**). Adverse health effects from repeated or prolonged exposure are not expected from normal use of the personal care products containing the assessed chemical at concentrations of up to 33%.

No risks are identified for public health during this assessment that require specific risk management measures.

Workers

Reformulation workers may incidentally be exposed to the assessed chemical at up to 100% concentration during reformulation processes, mainly via the dermal route, while ocular and inhalation exposures are also possible. The assessed chemical is irritating to skin but not classifiable under GHS. To mitigate potential exposure to reformulation workers, control measures would be required (see **Means for managing risk**). It is anticipated by the applicant that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible.

Professional workers in cosmetic businesses may experience dermal and inhalation exposure to the assessed chemical during the use of personal care products containing the assessed chemical at up to 33% concentration. The professional workers may wear some personal protective equipment (PPE) including gloves, coveralls and safety glasses or face masks. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the same end use products containing the assessed chemical.

Environment

Summary of environmental hazard characteristics

According to the *Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals* (DCCEEW 2022) and based on the available data the chemical is:

- Not Persistent (not P)
- Not Bioaccumulative (not B)
- Not Toxic (not T)

Environmental hazard classification

No measured aquatic toxicity data were submitted for the assessed chemical. Therefore, the assessed chemical is not formally classified under GHS for acute and chronic aquatic toxicities (UNECE 2017).

Summary of environmental risk

The assessed chemical will be introduced as a component in personal care products. Use of these products is expected to result in the release of the assessed chemical “down the drain” and into the sewers. Consequently, the assessed chemical will be treated at sewage treatment plants (STPs) before release to surface waters.

The assessed chemical is not PBT and is hence unlikely to have unpredictable long-term effects (EPHC 2009). The available ecotoxicity information shows that the assessed chemical is not expected to be harmful to aquatic organisms up to its water solubility limit. Therefore, based on the low hazard, the environmental risk from the introduction of the assessed chemical can be managed.

Means for managing risk

Information relating to safe introduction and use

The following control measures could be implemented to manage the risk arising from exposure to the assessed chemical during reformulation:

- Use of engineering controls such as
  - automated and enclosed systems where possible
  - adequate workplace ventilation to avoid accumulation of vapours, mists or aerosols

- Use of safe work practices to
  - avoid contact with skin
  - avoid inhalation of mist or aerosols

Conclusions

The Executive Director is satisfied that the risks to human health or the environment associated with the introduction and use of the industrial chemical can be managed.

Note:

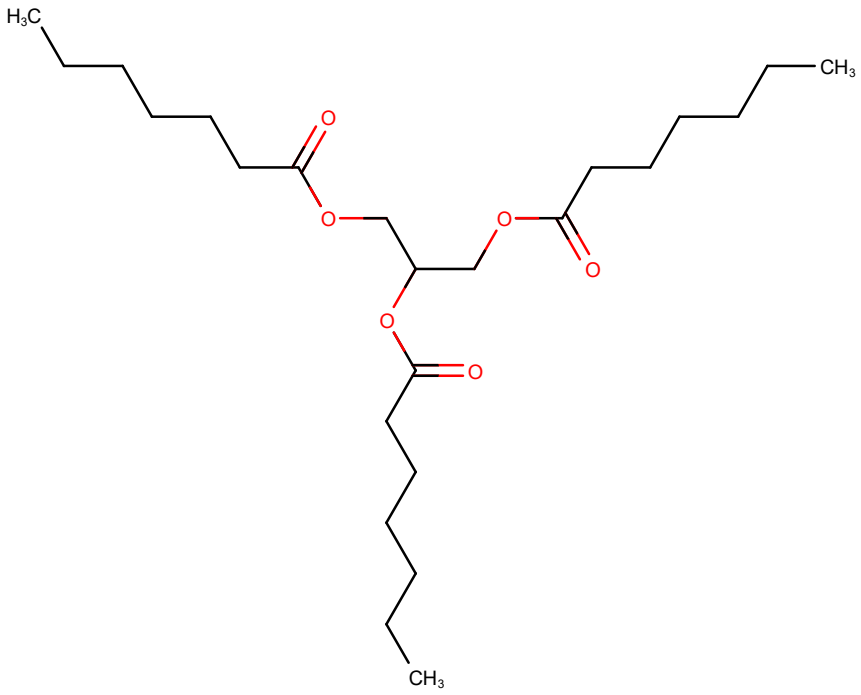
1. Obligations to report additional information about hazards under s 100 of *the Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	620-67-7
CAS name	Heptanoic acid, 1,1′,1″-(1,2,3-propanetriyl) ester
Molecular formula	$C_{24}H_{44}O_6$
Associated names	Heptanoic acid, 1,2,3-propanetriyl ester Heptanoin, tri-
Molecular weight (g/mol)	428.60
SMILES (canonical)	O=C(OCC(OC(=O)CCCCCC)COC(=O)CCCCCC)CCCCCC

Structural formula/Representative structure



Additional chemical identity information

The assessed chemical is a discrete chemical with a typical purity of 99.7%.

Relevant physical and chemical properties

Physical form	Clear liquid
Freezing point	< -40 °C

Boiling point	287 °C
Density	962 kg/m^3 at 25 °C
Vapour pressure*	4.35 x 10^{-8} kPa at 25 °C
Water solubility*	5 x 10^{-7} g/L at 25 °C
Flash Point	229 °C (Cleveland open cup)
Autoigintion temperature	267 °C at 97 kPa
Ionisable in the environment	No
log K_{ow}*	7.73
log K_{oc}*	5.58 (MCI method)

*Calculated using US EPI Suite v4.11(US EPA 2012)

Health hazard information

The toxicology information about the assessed chemical below is mainly taken from a journal article provided by the applicant (Fiume et al 2022), in which the purity of the test substance cannot be verified.

Toxicokinetics

A published clinical study in humans reported that the assessed chemical is extensively hydrolysed to glycerol and heptanoate in the gastrointestinal tract by pancreatic lipases, and subsequently heptanoate is absorbed through the gut wall. Heptanoate can diffuse across the mitochondrial membranes and undergo a series of beta-oxidative metabolic reactions to convert into energy (Lee et al 2021).

Acute toxicity

Based on the journal article provided by the applicant (Fiume et al 2022), median lethal dose (LD50) of the assessed chemical was > 5,000 mg/kg bw in NMRI mice for acute oral toxicity. The LD50 of the chemical was > 2,000 mg/kg bw (the highest dose tested) in rats for acute dermal toxicity.

Corrosion/Irritation

Skin irritation

In a 4-hour semi-occlusive patch test using 6 male White Russian rabbits with 0.5 mL of undiluted assessed chemical in accordance with OECD TG 404, very slight to slight erythema (scores of 1 - 2) was observed in all animals 30 - 60 minutes after patch removal. Moderate to severe erythema (scores of 3 - 4) and severe oedema (score of up to 4), with brown discolorations, dryness, sanguineous lacerations and scaling, were noted in 1 animal 24 - 72 hours after patch removal. Moderate redness of the skin, with dry skin and severe extensive

subcutaneous haemorrhage, was observed in 1 animal 72 hours after patch removal. Scaling was observed in all animals on day 6 after patch removal and all animals became normal on days 10 - 14. Full scores of the skin reaction were not reported in the journal article but can be verified in a REACH dossier (Fiume et al 2022, ECHA).

In a 4-hour semi-occlusive patch test using 3 male New Zealand White rabbits with 0.5 mL of undiluted assessed chemical in accordance with OECD TG 404, very slight erythema was observed in 1 animal and slight erythema was observed in 2 animals 1 hour after the patch removal. Very slight oedema in 1 animal, and very slight and slight erythema in 2 and 1 animals respectively, were observed 24 hours after patch removal. Very slight oedema was observed in 1 animal 48 hours after patch removal. There was very slight erythema in 2 animals, with very slight oedema in 1 animal 48 and 72 hours after patch removal. Full scores of the skin reaction were not reported in the article (Fiume et al 2022).

In a recent study, the assessed chemical was determined to be non-irritating to skin in an *in vitro* Reconstructed Human EpiDermis (RHE) Test (OECD TG 439). After 60-minute treatment with undiluted assessed chemical followed by a 42-hour post-exposure incubation, the relative mean viability of the treated skin model tissues was not altered by the treatment and was above the threshold of 50% for classification under GHS.

As shown above, 2 *in vivo* rabbit studies indicated skin irritation effects with 1 study demonstrating moderate to severe erythema and severe oedema with brown discolorations, dryness, sanguineous lacerations, severe extensive subcutaneous haemorrhage observed up to 72-hour time point in 1 animal. Scaling was observed in all animals on day 6 after patch removal. The purity of the test substance or scores of irritation were not fully reported in the journal article for the consideration of the severity of the skin effects. The recent *in vitro* study indicated no irritation according to the OECD TG 439 criteria. Based on the weight of evidence, the assessed chemical could be considered as a skin irritant but not meeting the GHS criteria for classification.

Eye irritation

Undiluted 0.1 mL of the assessed chemical was instilled into the eyes of male rabbits (n = 3) (OECD TG 405). It was reported as non-irritating to rabbit eyes (Fiume et al 2022).

Sensitisation

Skin sensitisation

The assessed chemical was tested using the Buehler test (OECD TG 406) with occlusive patches on female Dunkin Hartley guinea pigs (n = 20) at 100% concentration in both induction and challenge phases (Fiume et al 2022). There was no evidence of skin reactions indicative of sensitisation to the assessed chemical under the conditions of the test.

Repeat dose toxicity

Oral

In a 9-month feeding study (OECD TG not stated) using 3 groups of male Wistar rats (10 rats in each group), an oil containing 64% assessed chemical was not toxic and did not impact the growth, lipid digestibility, hepatic and renal function, and the lipid profile in serum analysis in the study (Fiume et al 2022). Under the experimental conditions, the oil containing the chemical

was reported to show a hepato-protector effect rather than a hepato-toxic effect. The NOAEL for the assessed chemical was estimated to be > 2,304 mg/kg bw/day.

Genotoxicity

Triglycerides, structurally similar to the assessed chemical, showed negative results in series of *in vitro* genotoxicity tests and in one *in vivo* bone marrow cytogenic study in rats (Fiume et al 2022). Based on the summary of genotoxicity results provided for triglycerides, the assessed chemical was not considered to be genotoxic.

Environmental exposure

The assessed chemical will be imported into Australia for reformulation into end-use personal care products. Reformulation will occur through a closed system. Significant release of the assessed chemical to the environment is not expected during reformulation, transport or storage. Release of the assessed chemical to the environment due to accidental spills is expected to be absorbed on suitable materials, and disposed of in accordance with relevant local, State, Territory and Federal regulations. Any unused product containing the assessed chemical is expected to be disposed of in accordance with relevant local, State, Territory and Federal regulations.

The assessed chemical is a component in personal care products. Use of these products is expected to result in the release of the assessed chemical “down the drain” and into the sewers. Consequently, the assessed chemical will be treated at sewage treatment plants (STPs) before release to surface waters.

Environmental fate

Partitioning

The assessed chemical has high log Koc value (log Koc = 5.58). Therefore, the chemical is expected to partition to and become immobile in soils and sediments.

The assessed chemical is very slightly water soluble (water solubility = 5 x 10^{-7} g/L at 25°C). If the assessed chemical is released to surface waters, the chemical is expected to partition to sediments based on its very slight water solubility, and high log Kow (log Kow = 7.73) and log Koc values.

The assessed chemical is very slightly volatile (vapour pressure = 4.35 x 10^{-8} kPa at 25°C). If the assessed chemical is treated by STPs, a minor proportion of the assessed chemical may partition to air during STP treatment based on SimpleTreat 3.0 model outputs (Struijs 1996).

Degradation

Based on measured biodegradability in water of an acceptable analogue chemical, and the assessed chemical’s predicted degradation in air, the assessed chemical is categorised as not persistent.

A biodegradability test conducted on an acceptable analogue chemical showed a 20-day Biological Oxygen Demand (BOD) to Chemical Oxygen Demand (COD) ratio of the test chemical higher than 80%. Thus, the assessed chemical is considered biodegradable in water.

Bioaccumulation

Based on available information, the assessed chemical is categorised as not bioaccumulative. In addition, available information on acceptable analogue chemicals also indicates that the assessed chemical is metabolised and has low potential for bioaccumulation (SIDS 2014).

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming 100% of the introduction volume is released into sewage treatment plants (STP) over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in STP processes is based on its physicochemical properties and biodegradability, modelled by SimpleTreat 3.0 (Struijs 1996) and is estimated to be 94%. Therefore 6% of the total introduction volume is estimated to be released to the aquatic environment.

The calculation of the PEC (Struijs 1996; EPHC 2009) is detailed in the table below:

Total Annual Import Volume	10,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	10,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	27.4	kg/day
Water use	200	L/person/day
Population of Australia	25.423	million
Removal within STP	94%	mitigation
Daily effluent production	5,085	ML/day
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	0.32	µg/L
PEC - Ocean	0.03	µg/L

Environmental effects

Effects on aquatic Life

Acute toxicity

The submitted model ecotoxicity data were predicted using ecological structure activity relationship ECOSAR v1.11 (US EPA 2012). The results show that the assessed chemical is not expected to be harmful to fish, aquatic invertebrates and algae up to its water solubility limit.

Predicted no-effect concentration (PNEC)

The predicted no-effect concentration (PNEC) has not been calculated as the assessed chemical is not expected to be harmful to aquatic organisms up to its water solubility limit.

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to the *Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals* (DCCEEW 2022) is presented below:

Persistence

Not Persistent (Not P). Based on measured biodegradability test of an acceptable read across chemical, the assessed chemical is categorised as Not Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on available information, the assessed chemical is categorised as Not Bioaccumulative.

Toxicity

Not Toxic (Not T). Based on predicted results of not harmful to aquatic organisms up to its water solubility limit, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

The assessed chemical is not PBT and is hence unlikely to have unpredictable long-term effects (EPHC 2009). The available ecotoxicity information shows that the assessed chemical is not expected to be harmful to aquatic organisms up to its water solubility limit. Therefore, based on the low hazard, the environmental risk from the introduction of the assessed chemical can be managed.

References

DCCEEW (Department of Climate Change, Energy, the Environment and Water) (2022), Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals, DCCEEW, accessed 23/07/2024.

ECHA (European Chemicals Agency), Propane-1,2,3-triyl trisheptanoate (CAS No. 620-67-7; Triheptanoin), Accessed 03/02/2025.

EPHC (Environment Protection and Heritage Council) (2009), Environmental Risk Assessment Guidance Manual for industrial chemicals, Prepared by: Chris Lee-Steere Australian Environment Agency Pty Ltd, February 2009. ISBN 978-1-921173-41-7.

Fiume MM, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks Jr JG, Shank RC, Slaga TJ, Snyder PW, Heldreth B (2022), Amended Safety Assessment of Triglycerides as Used in Cosmetics. *International Journal of Toxicology*, Vol. 41(Supplement 3) 22S–68S.

Lee SK, Gupta M, Shi J and McKeever K (2021), The pharmacokinetics of triheptanoin and its metabolites in healthy subjects and patients with long-chain fatty acid oxidation disorders. *Clinical Pharmacology in Drug Development*, 10(11):1325–1334.

SIDS (2014), Initial assessment profile of glycerides category, accessed 23/07/2024.

Struijs J (1996), SimpleTreat 3.0: a model to predict the distribution and elimination of chemicals by sewage treatment plants, National Institute of Public Health and the Environment.

UNECE (United Nations Economic Commission for Europe) (2017), Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Seventh Revised Edition, accessed 23/07/2024.

US EPA (2012), Estimation Programs Interface (EPI) SuiteTM for Microsoft Windows®, v 4.11, US EPA, accessed 15/09/2024.