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

Polymers with pendant acrylates

Evaluation statement

26 June 2023

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Polymers with pendant acrylates

Chemicals in this evaluation

Name	CAS registry number
Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)	28961-43-5
Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2,2-bis(hydroxymethyl)-1,3-propanediol (4:1)	51728-26-8
Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[ω-[(1-oxo-2-propen-1-yl)oxy]	52408-84-1
Poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)	53879-54-2
1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-, polymer with 2,2-bis(hydroxymethyl)-1,3-propanediol, 2-propenoate	56590-67-1
Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2,2-bis(hydroxymethyl)-1,3-propanediol (4:1), 2-propenoate	57679-22-8
1,3-Propanediol, 2,2-bis(hydroxymethyl)-, polymer with (chloromethyl)oxirane, 2-propenoate	57903-73-8
Oxirane, 2-(chloromethyl)-, polymer with .alpha.-hydro-.omega.-hydroxypoly[oxy(methyl-1,2-ethanediyl)], 2-propenoate	68130-31-4
Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate	68890-85-7
Poly[oxy(methyl-1,2-ethanediyl)], α,α′-(2,2-dimethyl-1,3-propanediyl)bis[ω-[(1-oxo-2-propen-1-yl)oxy]	84170-74-1
2-Oxepanone, homopolymer, ester with 2,2'-[oxybis(methylene)]bis[2-(hydroxymethyl)-1,3-propanediol], 2-propenoate	89800-10-2
2-Oxepanone, homopolymer, ester with 3-hydroxy-2,2-dimethylpropyl 3-hydroxy-2,2-dimethylpropanoate (2:1), di-2-propenoate	96915-49-0
2-Oxepanone, homopolymer, (tetrahydro-2-furanyl)methyl ester, 2-propenoate	96915-50-3
Poly[oxy(methyl-1,2-ethanediyl)], .alpha.,.alpha.',.alpha.''-1,2,3-propanetriyltris[.omega.-hydroxy-, di-2-propenoate	103534-15-2
Poly[oxy(methyl-1,2-ethanediyl)], .alpha.,.alpha.',.alpha.''-1,2,3-propanetriyltris[.omega.-hydroxy-, di-2-propenoate, hexanedioate (2:1)	103534-16-3
Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), bis[(diethylamino)propanoate] 2-propenoate	103694-82-2
Carbonic acid, diethyl ester, polymer with 1,6-hexanediol and 2-oxepanone, 2-propenoate	110081-37-3

Name	CAS registry number
Oxirane, methyl-, polymer with oxirane, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate	118800-30-9
1,3-Isobenzofurandione, hexahydro-, polymer with 2,2-bis(hydroxymethyl)-1,3-propanediol, 2-propenoate	120145-70-2
2-Oxepanone, homopolymer, 2-(5,5-dimethyl-1,3-dioxan-2-yl)-2-methylpropyl ester, 2-propenoate	120145-71-3
2-Oxepanone, homopolymer, 2-methyl-2-(4,4,6-trimethyl-1,3-dioxan-2-yl)propyl ester, 2-propenoate	120145-73-5
Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol,2-propenoate	120579-34-2
Poly[oxy(methyl-1,2-ethanediyl)], .alpha.,.alpha.',.alpha.''-1,2,3-propanetriyltris[.omega.-hydroxy-, 2-propenoate	123837-83-2
Hexanedioic acid, polymer with .alpha.,.alpha.',.alpha.''-1,2,3-propanetriyltris[.omega.-hydroxypoly[oxy(methyl-1,2-ethanediyl)]] and 1,3,5-tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione, 2-propenoate	123837-85-4
1,3-Propanediol, 2-ethyl-2-(hydroxymethyl)-, polymer with 2-(chloromethyl)oxirane, 2-propenoate	128819-84-1
2-Oxepanone, homopolymer, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, 2-propenoate	142540-43-0

The chemicals in this evaluation fall into 3 broad categories:

- alkoxylated polyols with pendant acrylates
- oxepanone-based polyesters with pendant acrylates
- isobenzofurandione-based polyesters with pendant acrylates.

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

Chemicals in this evaluation are polymers containing pendant acrylate (2-propenoate) groups. This evaluation is a human health risk assessment for all identified industrial uses of these polymers. The chemicals in this evaluation are likely to have similar use patterns. The toxicological properties are expected to mainly result from the pendant acrylate groups.

Summary of evaluation

Summary of introduction, use and end use

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

Based on international use information, the chemicals are reported to be used in paints and coatings, ink, toner and colourants, adhesive and sealants, and plastic and polymer

products. Based on the available information, these products are mainly used in professional settings with consumer uses not identified.

Human health

Summary of health hazards

Limited toxicological data are available for the chemicals in this evaluation. Polymer toxicity can be attributed to the presence of some specific functional groups present. Under the *Industrial Chemicals (IC) (General) Rules 2019* (IC Rules 2019), pendant acrylates are considered high concern reactive functional groups. The hazards of the polymers will depend on the number average molecular weight (Mn), functional group equivalent weight (FGEW) and the amount of low molecular weight species present. The available information indicates that the polymers are likely to be introduced and used with significant number of species below a molecular weight of 1000 Da. Where the polymers in this group are introduced as high molecular weight polymers with a low content of low molecular weight species, these chemicals are expected to have limited bioavailability and low hazard potential.

The critical health effects for risk characterisation are local effects.

Most of the data available are for alkoxylated polyols with pendant acrylates. Positive results were obtained from several in vivo skin sensitisation studies (GPMT, Buehler and LLNA). Limited data are available for the oxepanone- and isofurandione-based polymers with pendant acrylates. Based on the results of the adverse outcome pathway (AOP) assays and using the defined approach (DA) '2 out of 3' in the DASS Guideline (No: 497), an oxepanone-based polyester with pendant acrylates (CAS No. 89800-10-2) is a skin sensitiser. As the chemicals in this evaluation are likely to be introduced and used with significant number of species below a molecular weight of 1000 Da, they are all considered potential sensitisers.

In available in vivo skin irritation studies in rabbits, only slight effects were observed. However, some of the chemicals were considered to be skin irritants, warranting classification, based on in vitro skin irritation data.

In available in vivo eye irritation studies in rabbits, moderate eye irritant effects were observed (including corneal opacity scores equal to 1), warranting hazard classification. Effects were reversible within 14 days. Although the results from available in vitro eye irritation studies, did not meet classification criteria for eye irritation, based on a guide published by the European Chemical Industry Council (Cefic 2011), polymeric acrylates are recommended for classification for eye and skin irritation in the absence of toxicological data.

Based on the available data and read across data from polyol acrylates, chemicals in this evaluation are not expected to be genotoxic. These chemicals were largely negative in bacterial mutation assays although weak positive results were observed in *Salmonella typhimurium* strain TA1535. Positive results were reported in in vitro mammalian cell gene mutation tests in mouse lymphoma L5178Y cells. Negative results were reported in other in vitro studies. Negative results were reported in all in vivo studies.

Based on the available data chemicals in this evaluation have low acute oral toxicity. The common treatment related effects following repeated oral exposure included site of contact effects in the forestomach including inflammation, epithelial hyperplasia and hyperkeratosis, and stomach ulceration. Chemicals in this evaluation were reported to have a no observed adverse effect level (NOAEL) ranging from 40 mg/kg bw/day to 500 mg/kg bw/day in males

or females. These chemicals are not expected to cause specific adverse effects on fertility/sexual function and foetal development.

Limited data are available to evaluate carcinogenicity.

Hazard classifications relevant for worker health and safety

Chemicals in this evaluation satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards. If empirical data become available for a specific chemical, this data may be used to amend the default classification for that chemical. In addition, the classification does not apply if the polymer meets the definition of a polymer of low concern in the IC Rules 2019.

Health hazards	Hazard category	Hazard statement
Corrosion/irritation	Skin irrit. 2	H315: Causes skin irritation
Corrosion/irritation	Eye irrit. 2	H319: Causes serious eye irritation
Sensitisation	Skin sens. 1	H317: May cause an allergic skin reaction

Summary of health risk

Public

Based on the available use information, it is unlikely that the public will be exposed to chemicals listed in this evaluation. The public could come into contact with articles/coated surfaces containing these chemicals. However, it is expected that these chemicals will be bound within articles/coated surfaces and hence will not be bioavailable. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation, 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.

Chemicals in this evaluation are potential skin sensitisers and skin and eye irritants (Cefic 2011). The risks from exposure will depend on the Mn and the amount of low molecular weight species present in individual polymers. Polymers with low Mn (<1000 g/mol) and high amount of low molecular weight species present, may pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure to these such polymers should be implemented (see **Proposed means for managing risk**).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

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

The recommended classification and labelling entry should have the following note appended. 'Note 15: This chemical is a polymer. The hazards of a polymer may depend on several factors. For more information refer to the assessment report published on the website of the Australian Industrial Chemicals Introduction Scheme.

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 ocular and 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 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

Chemicals in this evaluation are polymers with pendant acrylates. Acylates are a high concern reactive functional group under the IC Rules 2019.

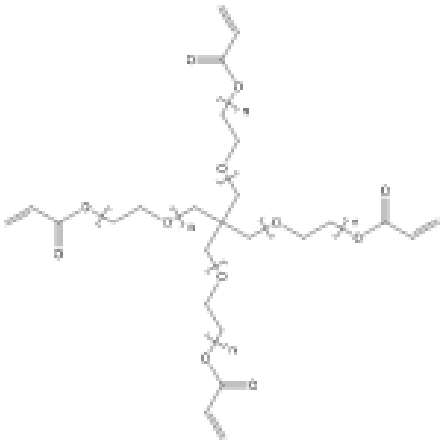
The polymers in this evaluation fall into 3 broad categories:

- alkoxylated polyols with pendant acrylates
- oxepanone-based polyesters with pendant acrylates
- isobenzofurandione-based polyesters with pendant acrylates.

Hazards of the polymers will depend on the Mn, FGEW and the amount of low molecular weight species present. Data available from the REACH dossiers for alkoxylated polyols with pendant acrylates indicate that these chemicals are typically manufactured and used with significant number of low molecular weight species below 1000 Da. For example, PETA-EPI-TTA (CAS No. 57903-73-8) is described in the REACH dossier as 'Reaction product of 1-chloro-2,3- epoxypropane (0–9 mol) with pentaerythritol and acrylic acid'. This would give a molecular weight range of approximately 390–915 g/mol. Limited data are available for oxepanone-based polyesters with pendant acrylates and isobenzofurandione-based polyesters with pendant acrylates. In the REACH dossier for CAS No. 89800-10-2, the molecular weight was reported to be in the range 524–1149. Based on information for similar polymers assessed under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), these polymers have potential to have Mn of <1000 Da. Therefore, the chemicals in this evaluation are likely to be introduced and used with significant number of low molecular weight species below 1000 Da.

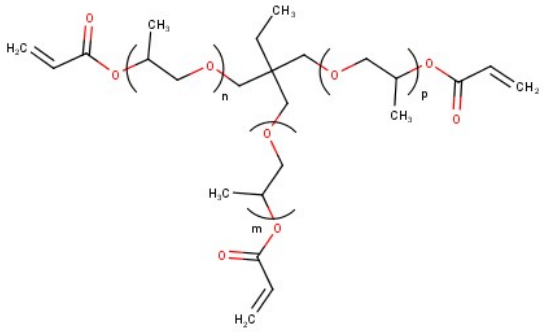
The evaluation includes 3 chemicals previously assessed under NICNAS, CAS Nos. 56590-67-1; 96915-49-0 and 120145-73-5. These are being reassessed together with similar polymers to consider new information.

Chemical identity

Chemical name	Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2,2-bis(hydroxymethyl)-1,3-propanediol (4:1)
CAS No.	51728-26-8
Synonyms	ethoxylated pentaerythritol tetraacrylate pentaerythritol ethoxylate tetraacrylate (PE(EO)TTA) pentaerythritol polyethylene glycol ether (1:4) tetraacrylate polyethylene glycol pentaerythritol ether tetraacrylate polyoxyethylpentaerythritol tetraacrylate tetramethylolmethane ethoxylate tetraacrylate tetramethylolmethane-initiated polyethylene glycol tetraacrylate
Molecular formula	(C2H4O)n(C2H4O)n(C2H4O)n(C2H4O)nC17H20O8
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylates
Structural formula:	

Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)
CAS No.	53879-54-2
Synonyms	trimethylolpropane propoxylate triacrylate (TMP(PO)TA) propoxylated trimethylolpropane triacrylate polypropylene glycol trimethylolpropane ether triacrylate poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-[(1-oxo-2-propenyl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol
Molecular formula	(C3H6O)n(C3H6O)n(C3H6O)nC15H20O6
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylates

Structural formula:



Chemical name	1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-, polymer with 2,2-bis(hydroxymethyl)-1,3-propanediol, 2-propenoate
CAS No.	56590-67-1
Synonyms	1,3-Propanediol, 2,2-bis(hydroxymethyl)-, polymer with 3a,4,7,7a-tetrahydro-1,3-isobenzofurandione, 2-propenoate
Molecular formula	(C8H8O3.C5H12O4)x.xC3H4O2
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	Isobenzofurandione-based polyester with pendant acrylates

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Chemical name	2-Oxepanone, homopolymer, ester with 3-hydroxy-2,2-dimethylpropyl 3-hydroxy-2,2-dimethylpropanoate (2:1), di-2-propenoate
CAS No.	96915-49-0
Synonyms	-
Molecular formula	C10H20O4.2(C6H10O2)x.2C3H4O2
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	oxepanone-based polyesters with pendant acrylates

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Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[ω-hydroxy-, hexanedioate (2:1), tetra-2-propenoate
CAS No.	103534-16-3
Synonyms	-
Molecular formula	(C3H6O)n(C3H6O)n(C3H6O)n(C3H6O)n(C3H6O)n(C3H6O)nC24H30O12
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

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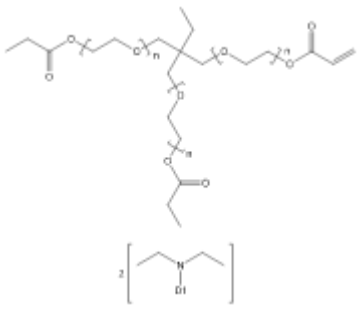
Chemical name	Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), bis[(diethylamino)propanoate] 2-propenoate
CAS No.	103694-82-2
Synonyms	-
Molecular formula	(C2H4O)n(C2H4O)n(C2H4O)nC23H42N2O6
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

Structural formula:



Chemical name	2-Oxepanone, homopolymer, 2-methyl-2-(4,4,6-trimethyl-1,3-dioxan-2-yl)propyl ester, 2-propenoate
CAS No.	120145-73-5
Synonyms	-
Molecular formula	C11H22O3.(C6H10O2)x.C3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	oxepanone-based polyester with pendant acrylate

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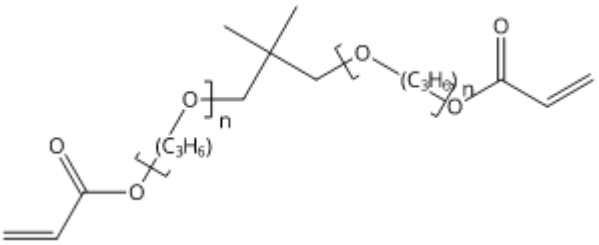
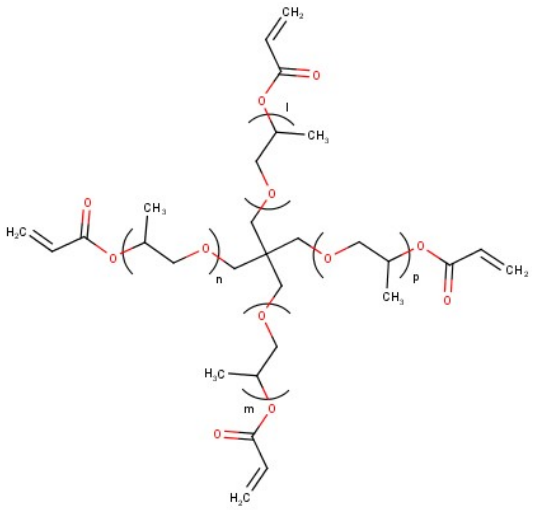
Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], α,α′-(2,2-dimethyl-1,3-propanediyl)bis[ω-[(1-oxo-2-propen-1-yl)oxy]
CAS No.	84170-74-1
Synonyms	neopentyl glycol propoxylate diacrylate (NPG(PO)DA)
	neopentyl glycol propyleneoxy diacrylate
	propoxylated neopentyl glycol diacrylate
	polypropylene glycol neopentyl glycol ether diacrylate
Molecular formula	(C3H6O)n(CH6O)nC11H16O4
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate
Structural formula:	

Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2,2-bis(hydroxymethyl)-1,3-propanediol (4:1), 2-propenoate
CAS No.	57679-22-8
Synonyms	propoxylated pentaerythritol acrylate
	propxylated pentaerythritol tetraacrylate (PE(POTTA)
Molecular formula	(C3H6O)n(C3H6O)n(C3H6O)n(C3H6O)nC5H12O4.xC3H4O2
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

Structural formula:

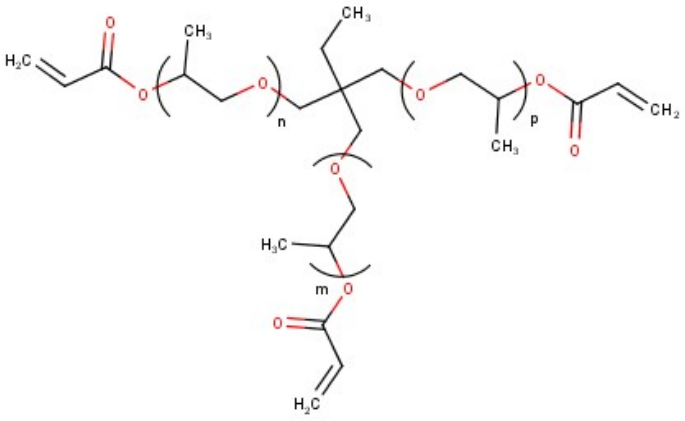


Chemical name	1,3-Propanediol, 2,2-bis(hydroxymethyl)-, polymer with (chloromethyl)oxirane, 2-propenoate
CAS No.	57903-73-8
Synonyms	1,3-propanediol, 2,2-bis(hydroxymethyl)-, polymer with (chloromethyl)oxirane, 2-propenoate oxirane, (chloromethyl)-, polymer with 2,2-bis(hydroxymethyl)-1,3-propanediol, 2-propenoate PE(EPI)TTA
Molecular formula	(C5H12O4.C3H5ClO)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate
CAS No.	68890-85-7
Synonyms	poly(propylene glycol) trimethylolpropane ether acrylate poly(propylene oxide) trimethylolpropane ether acrylate propoxylated trimethylolpropane acrylate (TMP(PO)TA)
Molecular formula	(C3H6O)n(C3H6O)n(C3H6O)nC6H14O3.xC3H4O2

Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

Structural formula:



Chemical name	2-Oxepanone, homopolymer, ester with 2,2'-[oxybis(methylene)]bis[2-(hydroxymethyl)-1,3-propanediol], 2-propenoate
CAS No.	89800-10-2
Synonyms	-
Molecular formula	-
Molecular weight (g/mol)	-
SMILES	-
Chemical description	oxepanone-based polyester with pendant acrylate

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Chemical name	2-Oxepanone, homopolymer, (tetrahydro-2-furanyl)methyl ester, 2-propenoate
CAS No.	96915-50-3
Synonyms	-
Molecular formula	(C6H10O2)x.C5H10O2.C3H4O2
Molecular weight (g/mol)	288.34
SMILES	-
Chemical description	oxepanone-based polyester with pendant acrylate

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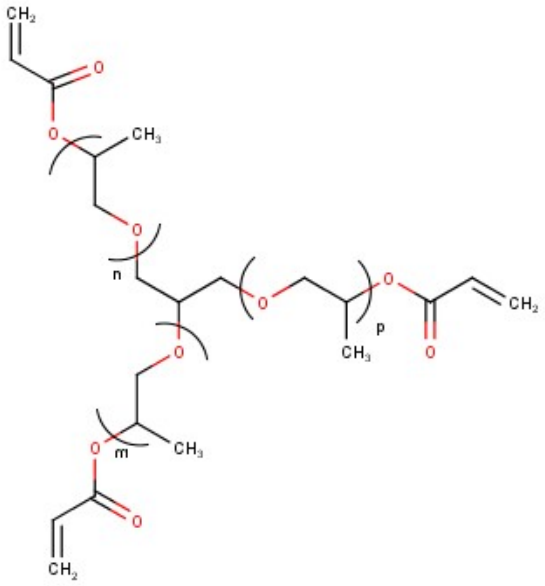
Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], .alpha.,.alpha.',.alpha.''-1,2,3-propanetriyltris[.omega.-hydroxy-, di-2-propenoate
CAS No.	103534-15-2
Synonyms	propoxylated glycerol diacrylate
Molecular formula	(C3H6O)n(C3H6O)n(C3H6O)nC9H12O5
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

Structural formula:



Chemical name	Carbonic acid, diethyl ester, polymer with 1,6-hexanediol and 2-oxepanone, 2-propenoate
CAS No.	110081-37-3
Synonyms	1,6-hexanediol, polymer with diethyl carbonate and 2-oxepanone, 2-propenoate 2-oxepanone, polymer with diethyl carbonate and 1,6-hexanediol, 2-propenoate
Molecular formula	(C6H14O2.C6H10O2.C5H10O3)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	oxepanone-based polyester with pendant acrylate

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Chemical name	Oxirane, methyl-, polymer with oxirane, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate
CAS No.	118800-30-9
Synonyms	oxirane, methyl-, polymer with oxirane, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate (9CI) oxirane, polymer with methyloxirane, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate (9CI) ethylene oxide-propylene oxide copolymer ether trimethylolpropane with acrylate trimethylolpropane-initiated ethylene oxide-propylene oxide copolymer acrylate
Molecular formula	C6H14O3.3(C3H6O.C2H4O)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

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Chemical name	1,3-Isobenzofurandione, hexahydro-, polymer with 2,2-bis(hydroxymethyl)-1,3-propanediol, 2-propenoate
CAS No.	120145-70-2
Synonyms	1,3-propanediol, 2,2-bis(hydroxymethyl)-, polymer with hexahydro-1,3-isobenzofurandione, 2-propenoate
Molecular formula	(C8H10O3.C5H12O4)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	isobenzofurandione-based polyester with pendant acrylate

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Chemical name	2-Oxepanone, homopolymer, 2-(5,5-dimethyl-1,3-dioxan-2-yl)-2-methylpropyl ester, 2-propenoate
CAS No.	120145-71-3
Synonyms	-
Molecular formula	C10H20O3.(C6H10O2)x.C3H4O2
Molecular weight (g/mol)	374.47
SMILES	-
Chemical description	oxepanone-based polyester with pendant acrylate

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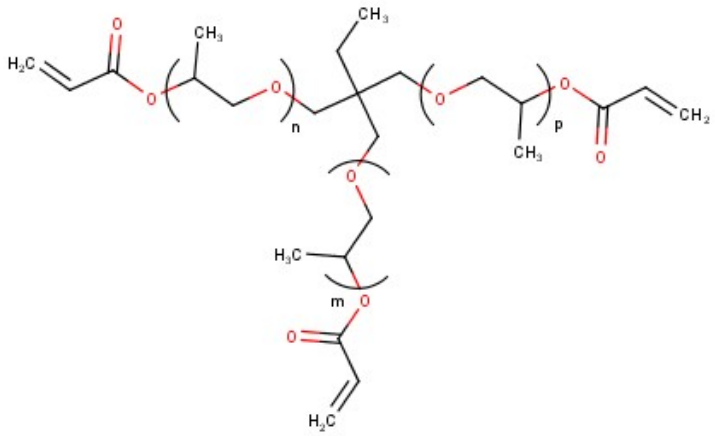
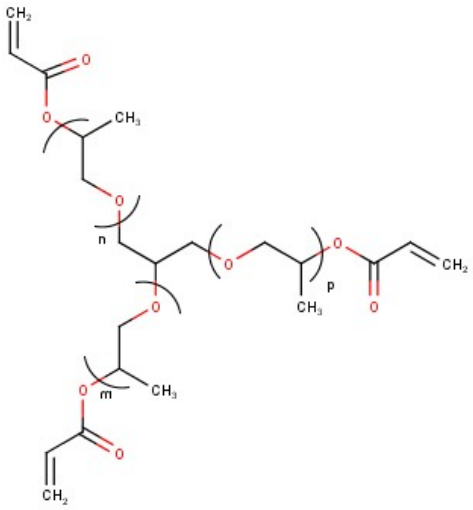
Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol,2-propenoate
CAS No.	120579-34-2
Synonyms	-
Molecular formula	C6H14O3.x(C3H6O)nH2O.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

Structural formula:



Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], .alpha.,.alpha.',.alpha.''-1,2,3-propanetriyltris[.omega.-hydroxy-, 2-propenoate
CAS No.	123837-83-2
Synonyms	-
Molecular formula	(C3H6O)n(C3H6O)n(C3H6O)nC3H8O3.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate



Structural formula:

Chemical name	Hexanedioic acid, polymer with .alpha.,.alpha.',.alpha.''-1,2,3-propanetriyltris[.omega.-hydroxypoly[oxy(methyl-1,2-ethanediyl)]] and 1,3,5-tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione, 2-propenoate
CAS No.	123837-85-4
Synonyms	1,3,5-triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris(2-hydroxyethyl)-, polymer with hexanedioic acid and α,α′,α″-1,2,3-propanetriyltris[ω-hydroxypoly[oxy(methyl-1,2-ethanediyl)]], 2-propenoate poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[o-hydroxy-, polymer with hexanedioic acid and 1,3,5-tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione, 2-propenoate
Molecular formula	(C9H15N3O6.C6H10O4.(C3H6O)n(C3H6O)n(C3H6O)nC3H8O3)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

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Chemical name	2-Oxepanone, homopolymer, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, 2-propenoate
CAS No.	142540-43-0
Synonyms	-
Molecular formula	C6H14O3.x(C6H10O2)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	oxepanone-based polyester with pendant acrylate

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Chemical name	Oxirane, 2-(chloromethyl)-, polymer with .alpha.-hydro-.omega.-hydroxypoly[oxy(methyl-1,2-ethanediyl)], 2-propenoate
CAS No.	68130-31-4

Synonyms	oxirane, (chloromethyl)-, polymer with α-hydro-ω-hydroxypoly[oxy(methyl-1,2-ethanediyl)], 2-propenoate poly[oxy(methyl-1,2-ethanediyl)], α-hydro-ω-hydroxy-, polymer with (chloromethyl)oxirane, 2-propenoate
Molecular formula	((C3H6O)nH2O.C3H5ClO)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

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Chemical name	1,3-Propanediol, 2-ethyl-2-(hydroxymethyl)-, polymer with 2-(chloromethyl)oxirane, 2-propenoate
CAS No.	128819-84-1
Synonyms	1,3-propanediol, 2-ethyl-2-(hydroxymethyl)-, polymer with (chloromethyl)oxirane, 2-propenoate oxirane, (chloromethyl)-, polymer with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, 2-propenoate TMP-EPI-TA
Molecular formula	(C6H14O3.C3H5ClO)x.xC3H4O2
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate

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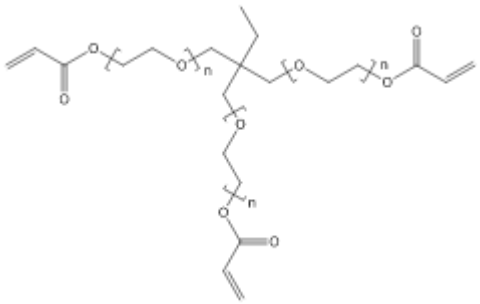
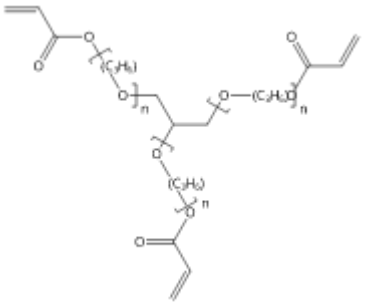
Chemical name	Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)
CAS No.	28961-43-5
Synonyms	ethoxylated trimethylolpropane triacrylate (TMP(EO)TA) ethoxylated trihydroxymethylpropane triacrylate 1,3-propanediol, 2-ethyl-2-(hydroxymethyl)-, triether with polyethylene glycol monoacrylate acrylic acid, triester with polyethylene glycol triether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol

	glycols, polyethylene, triether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, triacrylate
	poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propenyl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)
Molecular formula	(C2H4O)n(C2H4O)n(C2H4O)nC15H20O6
Molecular weight (g/mol)	-
SMILES	-
Chemical description	alkoxylated polyol with pendant acrylate
Structural formula:	

Chemical name	Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[ω-[(1-oxo-2-propen-1-yl)oxy]
CAS No.	52408-84-1
Synonyms	polypropylene glycol glycerol ether triacrylate
	polypropylene glycol-glycerin ether triacrylate
	propoxylated glycerin triacrylate
	propoxylated glycerol triacrylate
	propoxylated glycerol triacrylate copolymer
	propoxylated glyceryl triacrylate
	glycerol propoxylate triacrylate (G(PO)TA)
Molecular formula	(C3H6O)n(C3H6O)n(C3H6O)nC12H14O6
Molecular weight (g/mol)	-
SMILES	-

Chemical description alkoxylated polyol with pendant acrylate

Structural formula:



Introduction and use

Australia

No specific information is available on the introduction and use of these chemicals in Australia.

International

Limited specific information is available on the introduction use and end use of these chemicals internationally. The following international uses have been identified from the European Union Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers and the Substances in Preparations in Nordic Countries (SPIN n.d.) database for several of the polymers in this group:

- paints and coating products
- adhesive and sealant products
- plastic and polymer products
- ink, toner and colourant products.

No consumer uses were identified in the REACH dossiers and the chemicals were not listed on the North American consumer database (DeLima Associates n.d.).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for the chemicals in this evaluation.

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

No specific exposure standards were identified for the chemicals in this evaluation.

Health hazard information

In the REACH dossiers, the level of alkoxylation of the polymers as described in industry submitted REACH dossiers, is as follows:

- TMP(EO)TA (CAS No. 28961-43-5): 1–6.5 moles ethoxylated (REACHe n.d.)
- PE(EO)TTA (CAS No. 51728-26-8): 1–8.5 moles ethoxylated (REACHg n.d.)
- G(PO)TA (CAS No. 52408-84-1): 1–6.5 moles propoxylated (REACHf n.d.)
- PE-EPI-TTA (CAS No. 57903-73-8)—Reaction product of 1-chloro-2,3-epoxypropane (0–9 mol) with pentaerythritol and acrylic acid (REACHa n.d)

In the REACH dossier for TMP-EPI-TA (CAS No. 128819-84-1) the chemical is described as 'Reaction products of trimethylolpropane triglycidyl ether and acrylic acid' with a molecular weight of 390–611 g/mol (REACHd n.d.).

In the REACH dossier for CAS No. 89800-10-2 the molecular weight range was reported in the range 524–1149 (REACHc n.d.)

The above chemical composition is assumed to be the test material for these chemicals in the studies described below unless otherwise stated.

In the REACH dossier for TMP(PO)TA (CAS No. 68890-85-7) (REACHb n.d.) the identity of the test material was not specifically stated. However, the described constituents matched the description of the composition of TMP(PO)TA (CAS No. 68890-85-7). Therefore, in the studies below, the test material has been cited as TMP(PO)TA (CAS No. 68890-85-7).

Information on genotoxicity and systemic toxicity is also provided for the following polyol acrylates:

- tripropylene glycol diacrylate (TGPDA)—CAS No. 42978-66-5
- 2-propenoic acid reaction products with pentaerythritol (comprises PETtA/PETA)—(CAS No. 1245638-61-2)
- pentaerythritol triacrylate (PETA)—CAS No. 3525-68-3
- trimethylolpropane triacrylate (TMPTA)—CAS No.15625-89-5.

Toxicokinetics

No toxicokinetic data are available for this group of polymers. Absorption across biological membranes is dependent on the molecular weight of the specific polymer and percentage of low molecular weight species. Molecular weights below 500 Da are considered more likely to be absorbed, while molecular weights above 1000 Da are considered less likely to be absorbed. The polymers in this evaluation are most likely being introduced and used with significant number of species below a molecular weight of 1000 Da.

Once absorbed, acrylates are expected to be detoxified predominantly via conjugation with glutathione via the Michael addition reaction or by glutathione-S-transferase. The acrylates are also likely to be hydrolysed via carboxylesterases (Bingham and Cohrssen 2012).

Acute toxicity

Oral

Based on the available data, the chemicals are expected to have low acute oral toxicity. Median lethal dose (LD50) values for the following chemicals were reported to be >2000 mg/kg body weight (bw) in rats based on acute oral toxicity studies reported as compliant with good laboratory practice (GLP) and conducted in accordance with OECD TGs 423, 420 or 401 (REACHa n.d; REACHb n.d.; REACHc n.d.; REACHd n.d; REACHe n.d.; REACHf n.d.; REACHg n.d.):

- PE-EPI-TTA (CAS No. 57903-73-8)
- TMP(PO)TA CAS No. 68890-85-7
- TMP-EPI-TA (CAS No.128819-84-1)
- an oxepanone-based polyester with pendant acrylates (CAS No. 89800-10-2)
- TMP(EO)TA (CAS No. 28961-43-5)
- G(PO)TA (CAS No. 52408-84-1)
- PE(EO)TTA (CAS No. 51728-26-8).

For TMP(EO)TA (CAS No. 28961-43-5), one male died at 3200 mg/kg bw, with clinical signs of toxicity including piloerection, hunched posture, walking on toes, abnormal faeces, ungroomed appearance, and increased salivation in the 2 animals administered this dose. Macroscopic examination of the deceased animal revealed congestive changes (characterised by dark appearance/prominent blood vessels) in the subcutaneous tissue, brain, heart, liver and spleen. Congestion with gaseous distension and fluid contents were also noted in the stomach and in the alimentary tract (REACHe n.d.).

For the chemical TMP-EPI-TA (CAS No. 128819-84-1), clinical signs of toxicity were reported in animals at 5000 mg/kg bw, including decreased activity (4/5 observations), vocalisation (3/5), tremor (1/5), abnormal gait (3/5), bedding digging (1/5) and closed eyes (3/5) (REACHd n.d.).

Dermal

Limited data are available for the chemicals.

In an acute dermal toxicity study, reported as GLP compliant and conducted in accordance with OECD TG 402, a single 2000 mg/kg bw dose of the chemical, PE-EPI-TTA (CAS No. 57903-73-8), was applied topically (semi-occlusive) on the skin of Wistar rats (5/sex/dose), for a 24 hour exposure period. No mortality or clinical signs of toxicity were observed. The LD50 for acute dermal toxicity was reported to be >2000 mg/kg bw (REACHa n.d.).

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD TG 402, a single dose of 2000 mg/kg bw PE(EO)TTA (CAS No. 51728-26-8) (undiluted) applied dermally (semi-occlusive) on the skin of CRL:(WI) Wistar rats (5/sex/dose), for a 24 hour exposure period). No mortality and clinical signs were observed. The LD50 for acute dermal toxicity was >2000 mg/kg bw (REACHg n.d).

In a non-GLP compliant and non-guideline acute dermal toxicity study, TMP(EO)TA (CAS No. 28961-43-5) was applied on the skin of albino rabbits (strain and sex unspecified; 4/sex/dose) at a single dose of 13200 mg/kg bw (exposure duration unspecified). No mortality was observed. Lack of food consumption was reported in one animal. The LD50 for acute dermal toxicity was reported to be 13200 mg/kg bw (REACHe n.d.).

In a non-GLP compliant and non-guideline acute dermal toxicity study, G(PO)TA (CAS No. 52408-84-1) was applied on the skin (occlusive) of New Zealand White (NZW) rabbits at a dose of 2000 mg/kg bw. Moderate to severe erythema and oedema were observed at the site of application in 7/10 animals. Small areas of necrosis at the site of application were also observed in most animals with subsequent eschar formation and exfoliation. All 10 animals exhibited decreased food consumption from days 2–3 of treatment. One male had a swollen scrotum from days 2–5. Other clinical signs included nasal or ocular discharge and faecal staining. The LD50 for acute dermal toxicity was >2000 mg/kg bw (REACHf n.d.).

Inhalation

No data are available for the chemicals in this evaluation.

Corrosion/Irritation

Skin irritation

In vitro

In vitro studies reported to be GLP compliant and conducted in accordance with OECD TG 431 were reported for the following chemicals:

- PE-EPI-TTA (CAS No. 57903-73-8) was applied to reconstructed human epidermis EpiDerm™SCT for 3 and 60 minutes. The mean tissue viability was 96% and 100% after 3 and 60 minutes, respectively. Based on the measured viability (substance tissue viability of ≥50% after 3 minutes exposure and ≥15% after 60 minutes exposure), the chemical is considered non-corrosive (REACHa n.d.)
- TMP-EPI-TA (CAS No. 128819-84-1) was applied to reconstructed human epidermis EpiSkin™ for 3, 60 and 240 minutes. The mean tissue viability was 105%, 111% and 79% after 3, 60 and 240 minutes, respectively. Based on the measured viability, the chemical is considered non-corrosive (REACHd n.d.)
- PE(EO)TTA (CAS No. 51728-26-8) was applied to reconstructed human epidermis EpiSkinSM for 4 hours. The mean tissue viability was 92% after 4 hours. Substances that reduce viability to less than 35% after 240 minutes are classified as corrosive. Based on the measured viability, the chemical is considered non-corrosive.

In vitro skin irritation assay, reported as GLP compliant and conducted in accordance with OECD TG 439 (in vitro reconstructed human epidermis (RHE) test method for skin irritation), was reported for the following chemicals in this group:

- TMP(PO)TA (CAS No. 68890-85-7) was applied to RHE, for an exposure period of 60 minutes, followed by a post-treatment incubation period of 42.5 hours. A mean tissue viability value of 96.5% was reported for the chemical in this study, and the results indicate that the chemical is not irritating to the skin (REACHb n.d.)
- TMP-EPI-TA (CAS No.128819-84-1) was applied to RHE, for an exposure period of 15 minutes, followed by a post-treatment incubation period of 42 hours. A mean tissue viability value of 12% was reported for the chemical, and the chemical was determined to be irritating to the skin based on cell viability of less than 50% (REACHd n.d.)
- PE(EO)TTA (CAS No. 51728-26-8) was applied to RHE, for an exposure period of 15 minutes, followed by an observation period of 42 hours. A mean tissue viability value of 33% was reported for the chemical in this study, and it was determined to be irritating to the skin (REACHg n.d).

Based on the results from the in vitro studies:

- TMP-EPI-TA (CAS No.128819-84-1) and PE(EO)TTA (CAS No. 51728-26-8) are considered to be irritant to skin (Category 2) in accordance with UN GHS
- TMP(PO)TA (CAS No. 68890-85-7) is considered a non-irritant to skin in accordance with UN GHS
- PE-EPI-TTA (CAS No. 57903-73-8) is considered unlikely to have potential to cause corrosion.

In vivo

In vivo skin irritation study conducted in accordance with OECD TG 404 were reported for the following chemicals:

- 2-Oxepanone, homopolymer, ester with 2,2'-[oxybis(methylene)]bis[2-(hydroxymethyl)-1,3-propanediol], 2-propenoate (CAS No. 89800-10-2) was applied on the skin of 2 male and 4 female NZW rabbits for 24 hours under occlusive conditions. Observations were recorded at 24 and 72 hours after application. Mean scores of 0.11 for erythema and 0 for oedema were reported. Signs of erythema were observed in intact skin but were fully reversible within 72 hours. Mean scores for erythema and oedema were not provided for abraded skin (REACHc n.d.)

- TMP(EO)TA (CAS No. 28961-43-5) was applied on the skin in albino rabbits for 4 hours. The following results (based on gradings at 24, 48, 72 hours) were reported (REACHe n.d.):

    - Mean erythema score of 0.33. The signs of erythema were reversible in all animals 3 days after removal of the patch. No signs of oedema were reported at any time (3 NZW, semi-occlusive conditions)
    - Mean scores for erythema and oedema were zero. There were no signs of irritation reported at any time (3 NZW, semi-occlusive conditions)
    - In non-GLP compliant studies, mean scores for erythema and oedema were zero. No signs of erythema or oedema were reported at any time (3 NZW/White Vienna rabbits, semi-occlusive).
- G(PO)TA (CAS No. 52408-84-1) was applied on the skin of 3 NZW rabbits for 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48, 72 hours, 7 and 14 days after patch removal. The following mean scores for individual animals based on gradings at 24, 48, 72 hours were reported as: 1, 0.7 and 0 for erythema, and 0, 0 and 0 for oedema, respectively. The erythema was reversible in all animals within 7 days. No further information was provided in the study (REACHf n.d.).

The following results were reported in other non-guideline studies in rabbits conducted using TMP(EO)TA (CAS No. 28961-43-5) (REACHe n.d.):

- Mean erythema and oedema scores of <2 in intact and abraded skin
- Mean erythema score of 0.08 (reversible in 72 hours) in intact skin. Mean oedema score of 0
- Mean erythema scores of 1.91 and mean, oedema score of 1.91
- Mean erythema score of 1.75 and mean oedema score of 0.5 in abraded skin.

Other supporting skin irritation studies conducted either in accordance with OECD TG 404 or other scientifically acceptable methods using G(PO)TA (CAS No. 52408-84-1) also reported either no signs of irritation or slight to moderate erythema and oedema in rabbits. None of the studies reported oedema (REACHf n.d.).

Eye irritation

In vitro

In vitro eye corrosivity/irritation studies, reported as GLP compliant and conducted according to OECD TG 437, were reported for the following chemicals:

- PE-EPI-TTA (CAS No. 57903-73-8) was applied to 3 bovine cornea per experiment. The mean in vitro irritancy score (IVIS) was 2.9. IVIS >55 is classified as causing serious eye damage and IVIS ≤3 is not classified as eye irritant in the GHS Criteria for classification and labelling of chemicals. Based on the criteria of the assay, the chemical is not classified as an eye irritant (REACHa n.d.)
- TMP(PO)TA (CAS No. 68890-85-7) was applied to 3 bovine cornea. The mean IVIS was -0.62 based on the criteria of the assay, the chemical was not classified as an eye irritant (REACHb n.d.)
- 2-oxepanone, homopolymer, ester with 2,2'-[oxybis(methylene)]bis[2-(hydroxymethyl)-1,3-propanediol], 2-propenoate (CAS No. 89800-10-2) was applied to 3 bovine cornea. The mean IVIS was 0.08. Based on the criteria of the assay, the chemical was not classified as an eye irritant (REACHc n.d.)

In another, ex vivo GLP compliant and non-guideline eye corrosivity/irritation study using EpiOcular human derived epidermal keratinocytes construct PE-EPI-TTA (CAS No. 57903-73-8) was applied on the whole tissue construct for 30 min. The mean tissue viability was reported as 99%. Based on the results, the substance was not an eye irritant in the EpiOcular™ eye irritation test under the conditions of the study (REACHa n.d.).

In vivo

In vivo eye irritation studies, reported as GLP compliant and conducted according to OECD TG 437, were reported for the following chemicals in this group:

In several studies TMP(EO)TA (CAS No. 28961-43-5) was instilled into the conjunctival sac of one eye for each of 3 albino rabbits. The eyes were rinsed after 24 hours and observed at 24, 48 and 72 hours. The following was reported (REACHe n.d.):

- Mean scores (NZW rabbits): corneal opacity 1/4, iritis 0.67/2, conjunctival redness 2.56/3 and chemosis 2.11/4. The irritation effects were reversible in all animals within 14 days
- Mean scores (Vienna White rabbits) for animal 1 were: corneal opacity 1/4, iritis 0.67/2, conjunctival redness 2.67/3 and chemosis 2/4. Mean scores for animal 2 were: corneal opacity 1/4, iritis 0/2, conjunctival redness 2.33/3 and chemosis 1.33/4. Mean scores for animal 3 were: corneal opacity 1/4, iritis 0.67/2, conjunctivae score 2/3 and chemosis 1.33/4. The irritation effects were reversible within 8–23 days in some animals
- Mean scores (NZW rabbits): corneal opacity 0.33/4, iritis 0.11/2, conjunctival redness 1.22/3, and chemosis 0.56/4. The observed effects were reversible in all animals within 7 days.

The chemical G(PO)TA (CAS No. 52408-84-1) was instilled into one eye for each of 3 NZW rabbits. The eyes were rinsed after 24 hours and observed at 1, 24, 48 and 72 hours. Mean scores for animal 1 were: corneal opacity 1/4, iritis 1/2, conjunctival redness 2/3 and chemosis 1.67/4. Mean scores for animal 2 were: corneal opacity 1/4, iritis 1/2, conjunctival redness 3/3 and chemosis 2.33/4. Mean scores for animal 3 were: corneal opacity 1/4, iritis 1/2, conjunctival redness 3/3 and chemosis 2/4. The observed effects were reversible in all animals within 14 days (REACHf n.d.).

In other in vivo studies reported as GLP compliant and conducted in non-guideline studies or in accordance with OECD TG 405 instillation of G(PO)TA (CAS No. 52408-84-1) on the conjunctival sac of rabbits caused moderate to severe corneal opacity, iritis, chemosis and conjunctival redness (scores ≥2) in 2/3 animals. However, the effects were reversible within 7–21 days (REACHf n.d.).

PE(EO)TTA (CAS No. 51728-26-8) was instilled into 1 eye for each of 3 NZW rabbits. The eyes were rinsed off after 24 hours and observed at 1, 24, 48 and 72 hours. The following mean scores were reported: corneal opacity 2/4 (fully reversible in 21 days), iritis 0.67/2 ((fully reversible in 7 days), conjunctival redness 3/3 (fully reversible in 14 days) and chemosis 3.67/4 (fully reversible in 21 days) (REACHg n.d.).

Sensitisation

Based on the available data, the chemicals in this evaluation have the potential to cause skin sensitisation. No data is available regarding respiratory sensitisation.

Skin sensitisation

In vitro

The chemical 2-Oxepanone, homopolymer, ester with 2,2'-[oxybis(methylene)]bis[2-(hydroxymethyl)-1,3-propanediol], 2-propenoate (CAS No. 89800-10-2) was tested using 2 in vitro cell based assays to evaluate skin sensitisation. These tests are part of Integrated Approach to Testing and Assessment (IATA) which address specific key events of the AOP leading to development of skin sensitisation (OECD 2021). The antioxidant response element (ARE)-Nrf2 luciferase assay aims to address the second key event (keratinocyte activation) of the AOP by measuring the expression of a reporter luciferase gene under the control of a promoter from the ARE, a responding gene known to be upregulated by contact sensitisers. This assay was conducted in accordance with OECD TG 442D at concentrations of 0.195 to 400 µM. The chemical induced significant luciferase activity with >1.5 fold increase in keratinocyte induction reported for the study (REACHc n.d.).

In a Human Cell Line Activation test (h-CLAT) conducted in accordance with OECD TG 442E, cells were treated with CAS No. 89800-10-2 at concentrations of 4.3–15.4 µg/mL in cell culture media for 24 hours. The activation of the monocytic cell line (THP-1) was quantified by measuring increased expression of the cell surface markers CD86 and CD54 using fluorescent antibodies. The relative induction of fluorescence intensity (RFI) corresponding to CD86 expression was greater than 150% for the majority of the tested concentrations except at 4.3 µg/mL (in both first and second tests) and 6.2 µg/mL (in first test). Cell viability was reported as <50% at 12.8 and 15.4 µg/mL in the first test. The RFI for CD54 expression was greater than 200% only at concentrations of 15.4 µg/mL (in both first and second tests). Only chemicals that induce an RFI signal of 150% or greater of CD86 or 200% or greater of CD54 are considered positive for skin sensitisation. Based on these results, the chemical is considered positive for monocyte activation (REACHc n.d.).

The results of these assays are considered using the applicable DA in the DASS Guideline for Classification and Labelling purposes. Based on the results of the AOP assays and using the DA ‘2 out of 3’ in the DASS Guideline (No: 497), the chemical is a skin sensitiser.

In vivo

Other chemicals in this evaluation were tested using in vivo studies and are reported as follows (where data are available):

Local lymph node assay (LLNA)

The following polymers were tested in LLNA assays:

- In an LLNA: BrDU-ELISA conducted in according to OECD TG 442B, CBA mice (5 females/dose) received topical applications of PE-EPI-TTA (CAS No. 57903-73-8) in dimethylformamide at 0, 5, 10 or 25% The reported stimulation indices (SI) were 1.0, 1.1 and 1.9 for concentrations of 5, 10 and 25%, respectively. The reported concentration producing 1.6-fold increase in lymphocyte proliferation (EC1.6) was 19.38% (w/w). A clear dose response was observed (REACHa n.d.).
- In an LLNA conducted in accordance with OECD TG 429, CBA/CaJ mice (4 females/dose) received topical applications of TMP(PO)TA (CAS No. 68890-85-7) in acetone/olive oil (4:1v/v) at dose concentrations of 0, 0.5, 1 or 2.5%. The reported SI were 0.7, 1.58 and 1.50 for concentrations of 0.5, 1 and 2.5%, respectively. The estimated concentration to produce a 3-fold increase in lymphocyte proliferation (EC3) value was not calculated. (REACHb n.d.). The chemical was not considered to be a skin sensitiser in this study; however, it was only tested up to 2.5%.
- In a GLP compliant LLNA conducted according to OECD TG 429, female CBA mice (6/dose) received topical applications at concentrations of 0, 3, 10 or 30% of the chemical TMP(EO)TA (CAS No. 28961-43-5) in acetone. The study was performed using the lymph node weight and lymph node cell count to assess cell proliferation along with ear weight and ear thickness measurements to determine the skin irritation potential of the chemical. The reported SI were 1.60, 1.64 and 1.94 for concentrations of 3, 10 and 30% of the chemical, respectively. A statistically significant increase in lymph node cellularity was observed at all doses. The threshold concentration for sensitisation induction was <3% under the test conditions chosen (REACHe n.d.).
- In a non-GLP compliant LLNA conducted similarly to OECD TG 429, female CBA mice (6/dose) received topical applications at concentrations of 0.1, 0.3, 1, 3, 10 and 30% of TMP(EO)TA (CAS No. 28961-43-5,described as TMP-3E0-TA) in acetone. The study was performed using the lymph node weight and lymph node cell count to assess cell proliferation along with ear weight and ear thickness measurements to determine the skin irritation potential of the chemical. The reported SI were 1.02, 1.32, 1.89, 2.4 and 2.88 for concentrations of 0.1, 0.3, 1, 2.4 and 10%, respectively. A statistically significant increase in lymph node cellularity but not in lymph node weight was observed for 0.3% test substance concentration. The threshold concentration for sensitisation induction was reported as greater than 0.3% but <1% under the test conditions chosen (REACHe n.d.).
- Other supporting non-guideline LLNA studies conducted as equivalent or similar to OECD TG 429 with limited study details for TMP(EO)TA (CAS No. 28961-43-5) reported statistically significant increases in lymph node weight and lymph node cell count at concentrations over 3% (REACHe n.d.).
- In an LLNA conducted in accordance to OECD TG 429, female CBA mice(6/dose), were topically applied with G(PO)TA (CAS No. 52408-84-1) at 0, 0.1, 0.3, 1, 3 or 10% in acetone. A statistically significant increase in lymph node cell count and lymph node weights at 1, 3 and 10% were reported as 1.86, 2.47 and 3.14 respectively. The chemical is reported to be a skin sensitiser under the conditions of the study (REACHf n.d.).

Guinea pig maximisation test (GPMT)

The following chemicals were tested in GPMT assays:

- In a guinea pig maximisation test (GPMT) reported to be conducted according to OECD TG 406, intradermal induction (single injection) was performed on female CRL:HA guinea pigs (10/dose (test substance) or 5/dose (control)) using 0 or 0.5% of TMP-EPI-TA (CAS No. 128819-84-1) in 5% (w/v) ethanol and 0.1% (w/v) Polysorbate

80 in physiological saline. This was followed by topical induction at 100% for 48 hours. The animals were topically challenged with the chemical at 100% and 50% in ethanol:sesame oil 1:3 mixture with 1% (w/v) Polysorbate 80. Positive reactions were reported in 90% of the animals induced intradermally with 0.5% and challenged with 100% of the chemical, and in 30–70% of the animals intradermally induced with 0.5% and challenged with 50% of the chemical. The chemical was reported to cause skin sensitisation (REACHd n.d.).

- In a in vivo skin sensitisation study, reported as GLP compliant and conducted in accordance with OECD TG 406 (Buehler test), female Dunkin Hartley guinea pigs (20/dose (test substance) or 10/dose (control)) were induced with the chemical TMP(EO)TA (CAS No. 28961-43-5) in water. The animals were first challenged with the chemical at 75% and then at 50% (in double distilled water) in the second challenge. At the 75 % challenge concentration, positive reactions were reported in 40% (8/20) and 30% (6/20) of the animals in the first and second measurements reading, respectively. After challenge at 50%, positive reactions were reported in 45% (9/20) and 15% (3/20) of the animals in the first and second reading measurements, respectively. The chemical was reported to be a skin sensitiser in this study (REACHe n.d.).
- In a non-GLP compliant GPMT conducted similarly to OECD TG 406, male Dunkin Hartley guinea pigs (10/dose (test substance) or 5/dose (control)) were induced intradermally at doses of G(PO)TA (CAS No. 52408-84-1) at 0 or 1% in Alembicol D and topically induced at 100%. The animals were topically challenged at doses of 10% and 20% Alembicol D. At 20% topical challenge, positive reactions were reported in all animals. However, the results are considered inconclusive because positive reactions were also observed in the negative control groups during challenge exposure (REACHf n.d).
- In a GPMT conducted according to OECD TG 406, 10 male Himalayan guinea pigs were intradermally induced using PE(EO)TTA (CAS No. 51728-26-8) at 5% in PEG 300, followed by topical induction with undiluted chemical. The animals were challenged with 5% of the chemical in PEG 300. No skin reactions were observed after the challenge (REACHg n.d).

Repeat dose toxicity

The chemicals in this evaluation were reported to have an NOAEL ranging from 40 mg/kg bw/day to 500 mg/kg bw/day in male and female rats. The common treatment related effects included site of contact effects in the forestomach including inflammation, epithelial hyperplasia and hyperkeratosis, and stomach ulceration.

Oral

Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate (CAS No. 68890-85-7)

In an oral repeated dose toxicity study combined with reproductive/developmental toxicity study, reported to be GLP compliant and conducted according to OECD TG 422, Wistar rats (10/sex/dose) received TMP(PO)TA (CAS No. 68890-85-7) in drinking water. Daily doses of 0, 50, 150 or 500 mg/kg bw/day were administered for a total of 35 days in males or 56 days in females (except when in labour). No treatment related effects were observed. The NOAEL was reported to be 500 mg/kg bw/day (REACHb n.d.).

Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1) (CAS No. 28961-43-5)

In a GLP compliant oral repeated dose toxicity study combined with the reproductive/developmental toxicity screening study conducted in accordance with OECD TG 422, Wistar rats (10/sex/dose) were administered a chemical that includes TMP(EO)TA (CAS No. 28961-43-5) via oral gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day for a total of 29 days for males or 51–55 days for females. Salivation was observed in all animals at the mid and high doses. At the mid dose group, salivation was observed from day 14 of treatment in both sexes. At 1000 mg/kg bw/day, salivation was noted in most males and females from days 6 and 8 of treatment, respectively. At 1000 mg/kg bw/day, rales was reported for 6 consecutive days in 2 males and 3 females. Two mortalities were reported in high dose group females, one of which was euthanised after showing signs of breathing abnormalities (i.e. gasping), hunched posture, closed eyes (ptosis), cold feet and excessive salivation. At necropsy the animal had an irregular surface of the forestomach and the intestines were distended with gas. Microscopic examination revealed luminal exudate and acute inflammation of the trachea which were considered to be gavage related. At the high dose group, body weight gain was reduced in males without change in food consumption. Histopathological findings included squamous cell hyperplasia, prominent hyperkeratosis, submucosal oedema, lymphogranulocytic inflammation, ulceration and erosion in the forestomach in males from 100 mg/kg bw/day and in females from 300 mg/kg bw/day. The LOAEL for males was 100 mg/kg bw/day and the NOAEL for females was 100 mg/kg bw/day based on abnormal findings in the forestomach (REACHe n.d.).

Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[ω-[(1-oxo-2-propen-1-yl)oxy] (CAS No.52408-84-1)

In a repeated dose toxicity study combined with reproductive/developmental toxicity screening study reported as GLP compliant and conducted in accordance with OECD TG 422, Wistar rats (10/sex/dose) were administered an analogue chemical (CAS No. 42978-66-5) by gavage at doses of 0, 40, 125 or 375 mg/kg bw/day for a total of 29 days for males or 50–62 days for females. One female in the control group was euthanised due to total litter loss which the authors did not consider to be treatment related. Histopathologic findings observed included squamous cell hyperplasia, ulcers and inflammation in the forestomach in males at doses of 125 and 375 mg/kg bw/day and in females at 375 mg/kg bw/day. Hepatocellular hypertrophy in the liver in males was observed at 375 mg/kg bw/day which correlated with increased liver weight. The incidence and severity of hyaline droplet accumulation in the kidneys was observed in males at 375 mg/kg bw/day. The NOAEL was determined to be 40 mg/kg bw/day in males and 125 mg/kg bw/day in females due to histopathological changes in the forestomach (REACHf n.d.).

In a GLP compliant repeat dose toxicity study conducted in accordance with OECD TG 408, Wistar rats (10/sex/dose) were administered G(PO)TA (CAS No. 52408-84-1) by oral gavage at 0, 50, 150 or 375 mg/kg bw/day for 90 days. Two mortalities occurred on day 81 at the high dose level (375 mg/kg bw/day), one of which was euthanised due to poor condition. Microscopic findings from both animals included erosion/ulcer in the nasal cavity, trachea and larynx, as well as inflammation and exudate in the nasal cavity, suggestive of gastroesophageal reflux and aspiration of the gastric content. At high dose (375 mg/kg bw/day), macroscopic changes in the non-glandular mucosa of the forestomach were reported in both sexes. Treatment related histopathological findings including squamous cell hyperplasia in the forestomach and erosion/ulcer of the non-glandular mucosa of the forestomach were also reported in mid dose (150 mg/kg bw/day) and high dose groups. The NOAEL was 50 mg/kg bw/day based on the observed histopathological changes in the forestomach at higher doses (REACHe n.d.; REACHf n.d.).

In a GLP compliant oral repeated dose toxicity study combined with the reproductive/developmental toxicity screening study conducted in accordance with OECD TG 422, Wistar rats (10/sex/dose) were gavaged with chemical G(PO)TA (CAS No. 52408-84-1) at doses of 0, 150, 375 or 750 mg/kg bw/day for a total of 29 days for males or 50-58 days for females A total of six animals died across all doses reported (2 males; 4 females); one male and one female had abnormal findings in the forestomach (750 mg/kg bw/day). In addition, 2 females were euthanised due to litter loss at doses 150 and 375 mg/kg bw/day. Treatment related increase in liver and kidney weights were observed in males at doses of 375 and 750 mg/kg bw/day. Microscopic finding of centrilobular hepatocellular hypertrophy correlated with the liver weight increase was reported. An increased incidence and severity of extramedullary haematopoiesis was observed in the spleen of females at 750 mg/kg bw/day. Gross findings included irregular surface of the forestomach in both sexes from 150 mg/kg bw/day, which correlated with the microscopic findings of squamous cell hyperplasia, hyperkeratosis, ulcers, lymphogranulocytic inflammation and oedema in the forestomach. Enlarged pancreatic lymph nodes were observed in both sexes from 150 mg/kg bw/day. The LOAEL was 150 mg/kg bw/day for both sexes based on mortalities and findings in the forestomach (REACHe n.d.; REACHf n.d.).

Dermal

No data are available to evaluate dermal repeat dose toxicity

Inhalation

No data are available to evaluate respiratory repeat dose toxicity

Genotoxicity

Based on the available data and read across data from polyol acrylates, the chemicals in this evaluation are not expected to be genotoxic. The chemicals were largely negative in bacterial mutation assays although weak positive results were observed in *S. typhimurium* strain TA1535. Positive results were reported in in vitro mammalian cell gene mutation tests in mouse lymphoma L5178Y cells. Negative results were reported in other in vitro studies. Negative results were reported in all in vivo studies.

In vitro

1,3-Propanediol, 2,2-bis(hydroxymethyl)-, polymer with (chloromethyl)oxirane, 2-propenoate (CAS No. 57903-73-8)

Negative results were reported for PE-EPI-TTA (CAS No. 57903-73-8) in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *Escherichia coli* WP2 with and without metabolic activation (S9) at concentrations up to 5000 µg/plate (REACHa n.d.). No in vivo studies were available for this chemical.

In vitro

Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate (CAS No. 68890-85-7)

Negative results were reported for the chemical TMP(PO)TA (CAS No. 68890-85-7) in the following in vitro genotoxicity studies (REACHb n.d.):

- a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 97a, TA 98, TA 100, TA 102 and TA 1535 with and without metabolic activation (S9) at concentrations up to 5000 µg/plate
- a mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster lung fibroblasts (V79) with and without metabolic activation at concentrations up to 300 µg/mL.

No in vivo studies were available for this chemical.

In vitro

2-oxepanone, homopolymer, ester with 2,2'-[oxybis(methylene)]bis[2-(hydroxymethyl)-1,3-propanediol], 2-propenoate (CAS No. 89800-10-2)

Negative results were reported for CAS No. 89800-10-2 in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvrA with and without metabolic activation at concentrations up to 5000 µg/plate (REACHc n.d.). No in vivo studies were available for this chemical.

In vitro

1,3-Propanediol, 2-ethyl-2-(hydroxymethyl)-, polymer with 2-(chloromethyl)oxirane, 2-propenoate (CAS No. 128819-84-1)

Negative results were reported for the chemical TMP-EPI-TA (CAS No. 128819-84-1) in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvrA with and without metabolic activation (S9) at concentrations up to 5000 µg/plate (REACHd n.d.). No in vivo studies were available for this chemical.

In vitro

Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1) (CAS No. 28961-43-5)

Both positive and negative results were reported for the chemical TMP(EO)TA (CAS No. 28961-43-5 in the following in vitro studies (REACHe n.d.):

- Mostly negative results were reported in 4 separate bacterial reverse mutation assays (OECD TG 471) in *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvr A with and without metabolic activation at concentrations up to 5000 µg/plate. In one assay a positive reaction in strain TA 1535 was observed in the presence of metabolic activation.
- Positive results were reported in a mammalian gene mutation assay (OECD TG 476, non-guideline study) in the TK locus in mouse lymphoma cells L5178Y with and without metabolic activation at concentrations up to 55 µg/mL (experiment 1) and 60 µg/mL (experiment 2). The test substance induced weak but reproducible significant

dose-related increases in the mutant frequency both with and without metabolic activation, in both experiments. The mutagenic response was reported to be only observed in dose levels approaching the limit of acceptable toxicity.
- Positive results were reported in a mammalian gene mutation assay (OECD TG 476, non-guideline study) in the TK locus in mouse lymphoma cells L5178Y with metabolic activation at concentrations up to 20 nL/mL, but negative without metabolic activation.
- Negative results were reported in a mammalian gene mutation assay (OECD TG 476) in the HPRT locus in Chinese hamster lung fibroblasts (V79) with and without metabolic activation at concentrations up to 125 µg/mL.

No in vivo studies were available for this chemical**.**

In vitro

Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[ω-[(1-oxo-2-propen-1-yl)oxy] (CAS No. 52408-84-1)

Negative results were reported in the following genotoxicity studies for G(PO)TA (CAS No. 52408-84-1) (REACHf n.d.):

- Bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* WP2 uvr A with and without metabolic activation (S9) at concentrations up to 5000 µg/plate.
- Non-guideline bacterial reverse mutation assays in *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation (S9) at concentrations up to 150 000 µg/plate.
- Non-guideline mammalian chromosome aberration assay in human lymphocytes with and without metabolic activation at concentrations up to 8.0 µg/mL and 4.0 µg/mL, respectively.
- Mammalian gene mutation assay (OECD TG 476) in the HPRT locus in Chinese hamster lung fibroblasts (V79) with and without metabolic activation at concentrations up to 750 µg/mL and 100 µg/mL, respectively.

No in vivo studies were available for this chemical.

In vitro

Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2,2-bis(hydroxymethyl)-1,3-propanediol (4:1) (CAS No. 51728-26-8)

Positive and negative results were reported for PE(EO)TTA in the following genotoxicity studies (REACHg n.d):

- Negative results were reported in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA 98, TA 100, TA 102, TA 1535 and TA 1537 with and without metabolic activation (S9) at concentrations up to 5000 µg/plate
- Positive results were reported in mammalian gene mutation assay (OECD TG 476) in the TK locus in mouse lymphoma cells L5178Y with and without metabolic activation at concentrations up to 70 µg/mL.

In vivo

- Negative results were reported in the mammalian erythrocyte micronucleus tests reported as GLP compliant and conducted in accordance with OECD TG 474. NMRI mice (6/sex/dose) were treated with CAS No. 51728-26-8 in 40% ethanol and 60% polyethylene glycol by oral gavage at single doses of 437.5, 875 and 1750mg/kg bw. The incidence of micronucleated polychromatic erythrocytes in the bone marrow did not increase in any of the treatment groups, indicating a lack of clastogenicity (REACHg n.d.).

Polyol acrylates

The results from in vitro studies for tripropylene glycol diacrylate (TGPDA)—CAS No. 42978-66-5, pentaerythritol triacrylate (PETA)—CAS No. 3525-68-3 and trimethylolpropane triacrylate (TMPTA)—CAS No.15625-89-5 were similar to those observed for the chemicals in this evaluation. The chemicals were largely negative in bacterial mutation assays although weak positive results were observed in *S. typymurium* strain TA1535. Positive results were reported in in vitro mammalian cell gene mutation tests in mouse lymphoma L5178Y cells. Negative results were reported in other in vitro studies (NICNAS 2016; NICNAS 2017; REACHa).

In vivo

In the following mammalian micronucleus tests reported as GLP compliant and conducted in accordance with OECD TG 474, the incidence of micronucleated polychromatic erythrocytes in the bone marrow did not increase in any of the treatment groups indicating a lack of clastogenicity:

- TPDGA (CAS No. 42978-66-5) in olive oil administered by intraperitoneal injection at single doses of 0, 87.5, 175 or 350 mg/kg bw in NMRI mice (5 males/dose) (NICNAS 2016)
- TPGDA (CAS No. 42978-66-5) in corn oil administered by oral gavage at single doses of 0, 500, 1000 or 2000 mg/kg bw in CD-1 mice 5 males/dose (NICNAS 2016)
- PETA (CAS No. 3525-68) was applied dermally to B6C3F1 mice (10/sex/dose) the
- at doses of 0, 0.75, 1.5, 3, 6 or 12 mg/kg bw/day in acetone for 5 days/week for 14 weeks (REACHa n.d.).

Other negative in vivo studies include:

- TPGDA (CAS No. 42978-66-5) was applied dermally to Tg.AC mice (3 times/week for 20 weeks). Peripheral blood leukocytes were evaluated for DNA damage (single-strand breaks, alkali labile sites, DNA crosslinking) at weeks 4, 8, 12, 16, and 20 by using the alkaline (pH >13) single cell gel assay. The extent of DNA migration and the frequency of micronucleated PCE and NCE in blood were not altered (NICNAS 2016).

Carcinogenicity

Limited data are available on the chemicals in this evaluation to determine the potential for carcinogenicity. A 2 year dermal carcinogenicity study (OECD TG 451) for the polyol acrylate, TMPTA (CAS No. 15625-89-5), did not show carcinogenic effects in mice or rats

(NICNAS 2017). The polyol acrylate TGPDA (CAS No. 42978-66-5) may promote the induction of skin tumours. A non-genotoxic mechanism is considered likely (NICNAS 2016).

Reproductive and development toxicity

Based on the available data and read across data from polyol acrylates, the chemicals in this evaluation are not expected to cause specific adverse effects on fertility/sexual function and/or development.

Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-hydroxy-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1), 2-propenoate (CAS No. 68890-85-7)

In a repeated dose toxicity study combined with reproductive/developmental toxicity screening study reported as GLP compliant and conducted in accordance with OECD TG 422, Wistar rats (10/sex/dose) were administered TMP(PO)TA (in corn oil) by oral gavage. The doses were administered at concentrations of of 0, 50, 150 or 500 mg/kg bw/day for a total of 35 days in males and 56 days in females (except when in labour). One female parental animal in the high dose group (500 mg/kg bw/day) was sacrificed in a moribund condition on gestation day (GD) 24. Vaginal discharge and local inflammation in the uterus were observed from this animal. The local inflammation in the uterus was the cause of the moribund condition which was considered as being incidental and not related to treatment. The majority of parental animals of the high dose group showed salivation 2 hours after test administration which continued for several days of the study. Salivation was also observed in mid dose group 2 hours after treatment. Salivation was caused by the palatability of the chemical or localised effects in the upper digestive tract. No treatment related changes in body weight or body weight gain were observed for all dose groups in dams. Pup mortalities were reported on post-natal day (PND) 0 in the low and mid dose groups; however, this was considered to be incidental and unrelated to treatment. The mean number of delivered pups per dam, and the rate of liveborn and stillborn pups were within the normal range of biological variation in this strain of rats. The NOAEL reported for reproductive and foetal effects was 500 mg/kg bw/day (REACHb n.d.).

Poly(oxy-1,2-ethanediyl), α-hydro-ω-[(1-oxo-2-propen-1-yl)oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1) (CAS No. 28961-43-5)

In a non-guideline prenatal development toxicity study reported as GLP compliant, pregnant SD COBS CD rats (30/dose) were administered the chemical TMP(EO)TA (CAS No. 28961-43-5) by gavage at doses of 0 or 1000 mg/kg bw/day from GD 6 to 15. Two maternal mortalities were reported due to gavage error. A significant decrease in mean body weight gain was observed from GD 6–16. Clinical signs of maternal toxicity observed included salivation prior to and following dosing, urogenital matting, and hair loss from various body surfaces at the highest dose. No embryotoxic effects were apparent. No significant developmental adverse effects were reported in treatment groups. No significant or biologically meaningful differences in foetal abnormalities occurred in treatment groups compared with controls. The reported LOAEL for maternal and developmental effects was 1000 mg/kg bw/day (REACHe n.d.).

In a repeated dose toxicity study combined with reproductive/developmental toxicity screening study reported to be GLP compliant and conducted in accordance with OECD TG 422, Wistar rats (10/sex/dose) were administered TMP(EO)TA (CAS No.28961-43-5) as one of the constituents by oral gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day for a total of 29 days for males or 51–55 days for females (see **Repeated dose toxicity**). No treatment related reproductive and developmental effects were reported in any of the treatment groups.

The reported NOAEL for reproductive and developmental effects was 1000 mg/kg bw/day (REACHe n.d.).

Poly[oxy(methyl-1,2-ethanediyl)], α,α′,α″-1,2,3-propanetriyltris[ω-[(1-oxo-2-propen-1-yl)oxy (CAS No. 52408-84-1)

In a repeated dose toxicity study combined with the reproductive/development toxicity screening study reported as GLP compliant and conducted in accordance with OECD TG 422, Wistar rats (10/sex/dose) were administered the G(PO)TA (CAS No. 52408-84-1) at doses of 0, 150, 375 or 750 mg/kg bw/day for a total of 29 days for males or 50–58 days for females (see **Repeat dose toxicity**). No treatment related effects in reproductive parameters including precoital time, number of implantation sites and fertility indices were observed in any of the treatment groups. No treatment related effects were observed in the developmental parameters including post-implantation survival index, live birth index, live litter size, pup body weight and anogenital distance. The reported NOAEL for reproductive and developmental effects was 750 mg/kg bw/day (REACHf n.d.).

In a GLP compliant non-guideline prenatal development toxicity study, pregnant SD COBS CD rats (30/dose) were administered G(PO)TA (CAS No. 52408-84-1) at 0 or 1000 mg/kg bw/day from GD 6–15. Clinical signs of toxicity include salivation before and after administration of the chemical, urogenital matting and hair loss from various body areas were observed in dams. A significant decrease in mean body weight gain of dams was observed during GD 6–16. No treatment related changes in developmental parameters were reported. The LOAEL for maternal effects was 1000 mg/kg bw/day due to decreased body weight gain and the NOAEL for developmental effects was 1000 mg/kg bw/day (REACHf n.d.).

Polyol acrylates

In a repeated dose toxicity study combined with reproductive/developmental toxicity screening study reported as GLP compliant and conducted in accordance with OECD TG 422, 2-propenoic acid reaction products with pentaerythritol (CAS No. 1245638-61-2) (in corn oil) was administered once daily to Crl:CD(SD) rats (12/sex/dose) by oral gavage at doses of 0, 25, 75 or 200 mg/kg bw/day for a total of 28 days (males) or 40–47 days (females). No treatment related effects were observed on mating and fertility, male copulation, female conception indices, mean number of days between pairing and coitus, gestation length, and parturition at any dose level. Mean numbers of pups born, live litter size, mean pup body weights, and pup body weight gains were unaffected by treatment. No treatment related clinical findings or macroscopic findings for pups that were found dead were noted at any dose level. The NOAEL reported for both reproductive and foetal effects was 200 mg/kg bw/day (REACHa n.d.).

In a non-GLP compliant, non-guideline prenatal development toxicity study, pregnant CRL:COBS CD(SD) BR rats (n=25) were administered PETA (CAS No. 3525-68-3) (in corn oil) once daily at a dose of 10 mg/kg bw/day (negative control was unspecified) by oral gavage from GD 6–15. Dams were sacrificed on GD 20. One animal died on GD 15. There were no abnormal findings in the dam at necropsy Clinical signs of alopecia and wheezing were reported in treated dams. No treatment related effects on foetal viability, weights, visceral or skeletal abnormalities were observed. The NOAEL reported for developmental effects was 10 mg/kg bw/day (REACHa n.d.).

In an extended one-generation reproductive toxicity study reported to be GLP compliant conducted according to OECD TG 443, Wistar rats (25 (P) or 20 (F1)/sex/dose) were administered TGPDA (CAS No. 42978-66-5) by gavage at doses of 0, 10, 30 or 100 mg/kg

bw/day. The males were treated for 11–13 weeks and females were treated for 14–18 weeks. One female in the low dose group (10 mg/kg bw/day) was euthanised after total litter loss; however, the authors did not consider this effect to be related to treatment. Significant increase in urea, sodium and potassium levels were observed in the parental males at 30 or 100 mg/kg bw/day. However, these effects were not considered adverse because the values were slightly above the range considered normal (sodium) or remained within the normal range (urea and potassium) and not supported by microscopic findings. No treatment related changes in reproductive parameters were reported in the parental animals. Significantly increased neutrophil and lymphocyte counts were observed in the F1 males (Cohort 1A) at 100 mg/kg bw/day. The blood cell counts were within normal range and not correlated to microscopic findings. No treatment related developmental changes were reported in any dose groups. The NOAEL for reproductive and developmental effects was 100 mg/kg bw/day (REACHe n.d.).

In a prenatal developmental toxicity study reported to be GLP compliant conducted according to OECD TG 414, pregnant NZW rabbits (22/dose) were administered TGPDA (CAS No. 42978-66-5) by gavage at doses of 0, 50, 150 or 450 mg/kg bw/day from day 6 to 28 post-coitum. One female from the high dose group (450 mg/kg bw/day) was euthanised after 4 days of treatment due to moribund condition. At necropsy, red foamy content of the trachea, several reddish foci in left caudal lobe of the lungs and grey-white discolouration of the left caudal lobe of the lungs were observed reported to be indicative of complications during the oral gavage procedure. No treatment related maternal and foetal developmental changes were observed in any of the dose groups. The reported NOAEL for maternal and foetal developmental effects was 450 mg/kg bw/day (REACHe n.d.).

In a repeated dose toxicity study combined with reproductive/developmental toxicity screening study reported as GLP compliant and conducted in accordance with OECD TG 422, Wistar rats (10/sex/dose) were administered TGPDA (CAS No. 42978-66-5) by gavage at doses of 0, 40, 125 or 375 mg/kg bw/day for a total of 29 days for males or 50-62 days for females (see **Repeat Dose Toxicity**). No treatment related effects in reproductive parameters including mating index, precoital time, number of implantation sites and fertility index were observed in any of the dose groups. No treatment related effects were observed in developmental parameters including viability index, live litter size, pup body weight, areola/nipple retention and anogenital distance. The reported NOAEL for reproductive and developmental effects was 375 mg/kg bw/day (REACHf n.d.).

In a combined 28 day repeated dose and reproductive/developmental toxicity study (see **Repeated Dose Toxicity**), TMPTA (CAS No. 15625-89-5) was administered by oral gavage to 10 Crl:WI(Han) rats at dose levels of 30, 100 or 300 mg/kg/day (5/sex/dose level). Males were treated for 2 weeks prior to mating and during mating. The females were treated for 2 weeks prior to mating, during mating, during gestation, and up to at least day 4 of lactation. No treatment related effects in relation to reproduction (mating, fertility and conception indices, precoital time, number of corpora lutea and implantation sites) and developmental toxicity (gestation index and duration, parturition, maternal care and early postnatal pup development (mortality, clinical signs, body weight and macroscopy)) were seen. No morphological findings in the reproductive organs of either sex attributed to the chemical were found. Spermatogenic staging profiles were normal for all males examined. Based on these results, an NOAEL of 300 mg/kg bw/day for reproductive toxicity and for developmental toxicity was derived from this screening study (NICNAS 2017).

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