CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

2,2'-ethylenedioxydiethyl dimethacrylate

EC Number: **203-652-6**

CAS Number: **109-16-0**

Index Number: Not available

Contact details for dossier submitter: **Finnish Competent Authority
Finnish Safety and Chemicals
Agency (Tukes)
Finland**

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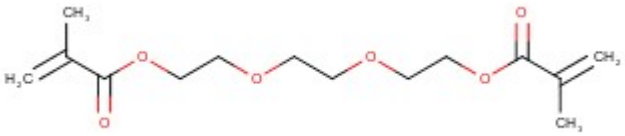
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	2,2'-ethylenedioxydiethyl dimethacrylate 2-(2-{2-[(2-methylprop-2-enoyl)oxy]ethoxy}ethoxy)ethyl 2-methylprop-2-enoate 2-Propenoic acid, 2-methyl-,1,2-ethanediylbis(oxy-2,1-ethanediyl)ester Triethyleneglycol dimethacrylate
Other names (usual name, trade name, abbreviation)	1,2-bis[2-(methacryloyloxy)ethoxy] ethane TRGDMA
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	203-652-6
EC name (if available and appropriate)	2,2'-ethylenedioxydiethyl dimethacrylate
CAS number (if available)	109-16-0
Other identity code (if available)	-
Molecular formula	C14H22O6
Structural formula	
SMILES notation (if available)	CC(=C)C(=O)OCCOCCOCCOC(=O)C(C)=C
Molecular weight or molecular weight range	286.32 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable (the structure of the substance does not demonstrate stereo-isomerism)
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable (the substance is not an UVCB)
Degree of purity (%) (if relevant for the entry in Annex VI)	95-99.68%

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
2,2'-ethylenedioxydiethyl dimethacrylate (CAS 109-16-0)	95-99.68%	No entry in Annex VI	Skin Sens. 1; H317 Skin Sens. 1B; H317 Aquatic Chronic 2; H411 Aquatic Chronic 3; H412 Eye Irrit. 2; H319 Skin Irrit. 2; H315 STOT SE 3; H335

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

No impurities relevant for classification.

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

No additives relevant for classification.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current entry in Annex VI										
Dossier submitters proposal	-	2,2'-ethylenedioxydiethyl dimethacrylate	203-652-6	109-16-0	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	-	2,2'-ethylenedioxydiethyl dimethacrylate	203-652-6	109-16-0	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	**Harmonized classification proposed**	**Yes**
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

For 2,2'-ethylenedioxydiethyl dimethacrylate there is no harmonized classification available, as the substance is not listed in Annex VI to the Regulation (EC) No 1272/2008 (CLP Regulation).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Differences in self-classification in the C&L Inventory

Disagreement by DS with current self-classification

Further detail on need of action at Community level

According to Article 36(3) of the CLP Regulation, for a substance that fulfills the criteria for other hazard classes or differentiations than those of CMR or respiratory sensitisation (Category 1) and the substance is not an active substance under the Plant Protection Product Directive (PPPD) and Biocidal Product Directive (BPD), a harmonized classification and labelling proposal can be submitted if a justification is provided demonstrating the need for such action at community level. There is no entry in Annex VI to the CLP Regulation for 2,2'-ethylenedioxydiethyl dimethacrylate and there have been no previous classification and labelling discussions of the substance.

As of August 2020, the C&L Inventory contains in total 183 notifications for 2,2'-ethylenedioxydiethyl dimethacrylate with respect to skin sensitisation:

- Skin Sens. 1 (163 notifications)
- Skin Sens. 1B (20 notifications)

Furthermore, 298 notifiers did not classify the substance for skin sensitisation at all. None of the notifiers has classified the substance as Skin Sens. 1A.

Differences in self-classification between different notifiers in the C&L Inventory have been discovered and the dossier submitter (DS) disagrees with the self-classifications Skin Sens. 1 and no classification proposed by the notifiers. 2,2'-ethylenedioxydiethyl dimethacrylate is registered under REACH, and it is manufactured and/or imported in the European Economic Area in 1 000-10 000 tonnes per year. The widespread use of the substance supports action at community level: exposure to 2,2'-ethylenedioxydiethyl dimethacrylate is anticipated under circumstances of professional, industrial and consumer use, mainly via dermal route. Workers may be in direct contact with formulated products containing the substance during mixing or blending, and the products may be used with rollers or brushes or via dipping or pouring. 2,2'-ethylenedioxydiethyl dimethacrylate is one of the most commonly patch tested (meth)acrylates that quite often induces positive reactions in clinical patients. There are over 500 published cases with a positive patch test reaction to the substance, which exceeds the limit for high frequency of occurrence of skin sensitisation.

5 IDENTIFIED USES

2,2'-ethylenedioxydiethyl dimethacrylate is used in adhesives and sealants. As a liquid monomer, it is used in applications that come into contact with skin or nails. It is used by consumers, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

6 DATA SOURCES

The REACH registration dossier of 2,2'-ethylenedioxydiethyl dimethacrylate was used as the main data source for this CLH report. In addition, full study reports, open literature publications and patient data from the Finnish Institute of Occupational Health were used.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid	REACH registration dossier	Observed
Melting/freezing point	Not determined	Anonymous 2007	Measured OECD TG 102/EU Method A.1 The test substance is reported to undergo glass transition (amorphous solidification) at -88°C.
Boiling point	Not determined	Anonymous 2007	OECD TG 103/EU Method A.2 (differential scanning calorimetry) No boiling point was detected prior to polymerisation of the substance.
Relative density	1.092 at 20°C	REACH registration dossier	Measured Value taken from handbook, no further details available on the used method.
Vapour pressure	0.077 Pa at 20 °C (read-across)	Anonymous 2011	Measured OECD TG 104/EU Method A.4 (effusion method/vapour pressure balance) Read-across data for the structurally similar ethyltriglycol methacrylate
Surface tension	Not assessed	REACH registration dossier	No surface activity is predicted based on the chemical structure of the test substance.
Water solubility	3.6 g/L at 20°C, pH 6.8	Anonymous 1988	Measured OECD TG 105 (flask method)
Partition coefficient n-octanol/water	Log P_{ow} 2.30 at 20 °C	Anonymous 2010	Measured OECD TG 117/EU Method A.8 (HPLC method)
Flash point	> 150°C at 1012.25 hPa	Anonymous 2008a	Measured EU Method A.9 (closed cup method)
Flammability	Not flammable	REACH registration	Study technically not feasible

Property	Value	Reference	Comment (e.g. measured or estimated)
		dossier	(the substance is a liquid).
Explosive properties	Not explosive	REACH registration dossier	There are no chemical groups associated with explosive properties present in the molecule.
Self-ignition temperature	255°C at 1025 hPa	Anonymous 2009	Measured EU Method A.15/DIN 51794
Oxidising properties	Not oxidising	REACH registration dossier	Oxidising properties are not expected on the basis of chemical structure.
Granulometry	Not applicable	REACH registration dossier	The substance is a liquid and marketed or used in a non solid or granular form.
Stability in organic solvents and identity of relevant degradation products	Not applicable	REACH registration dossier	The study does not need to be conducted because the stability of the substance is not considered to be critical.
Dissociation constant	Not applicable	REACH registration dossier	The substance does not contain any ionic, dissociable structures.
Viscosity	9.15 mm²/s at 20°C 4.88 mm²/s at 40°C	Anonymous 2008b	Measured OECD TG 114 (Micro-Ubbelohde viscometer)/DIN 51562

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Remarks	Results	Reference
Basic toxicokinetics in vitro Non-guideline GLP Key study Reliability: 2 Test material: triethylene glycol dimethacrylate Purity: not specified	Concentration: 0.25 mM Duration: 120 minutes (samples were collected at 0, 2, 5, 15, 30, 60 and 120 minutes) Vehicle: DMSO Positive control: methyl methacrylate Negative controls in the rat liver microsome experiments included incubations with heat-inactivated microsomes, no microsomes and no NADPH.	Test substance was rapidly converted to methacrylic acid (MAA) in whole rat blood and rat liver microsomes with hydrolysis half-lives of 5.68 minutes (blood) and 3.01 (liver microsomes). Absence of NADPH made little or no difference in hydrolysis rates. Heat inactivation significantly reduced the rates, and absence of microsomes resulted in no hydrolysis.	Anonymous (2013a)
Basic toxicokinetics in	Male albino rat 2 animals per dose	Excretion (after 24 hours): Dose (mg/kg | Amount of dose recovered	McKennis et al. (1961)

<table>
<tr><th>Method</th><th>Remarks</th><th>Results</th><th>Reference</th></tr>
<tr><td>vivo (elimination): administration of ^{14}C-triethylene glycol to the rat
Non-guideline
Non-GLP
Key study
Reliability: 2

Test material: ^{14}C-triethylene glycol (specific activity 5.13 µc/mg)
Purity: 99.9%</td><td>Doses: 0, 125, 140, 250 and 600 mg/kg bw/day
Administration: oral, by gavage
Vehicle: water</td><td><table><tr><td>bw/day)</td><td>in urine chloroform extracts (%)</td></tr><tr><td>125</td><td>66</td></tr><tr><td>140</td><td>65</td></tr><tr><td>250</td><td>38</td></tr><tr><td>600</td><td>27</td></tr></table>86-94% of the radioactivity was recovered in the urine in the subsequent 5-day period. The total excretion via urine and faeces amounted to 94-97%. The expired air over a 60-h period contained approximately 1% of the administered dose. The chromatograms of chloroform extracts of urine showed no evidence of ethylene glycol or diethyleneglycol.
One oxidation product is suggested to be a monocarboxylic acid which arises by metabolic oxidation of a single terminal hydroxyl group of the parent glycol. Triethylene glycol is expected to pass the organism without further metabolism.</td><td></td></tr>
<tr><td>Basic toxicokinetics in vitro and in vivo (read-across)
Non-guideline
GLP: not specified
Key study
Reliability: 1

Test material: methyl methacrylate (MMA)
Purity: > 99%</td><td>A series of in vitro and in vivo studies were used to develop PBPK models that predict the metabolism and fate of a series of methacrylates

Administration: i.v. injection

Liver microsome studies: human, rat
Dermal absorption studies: rat skin (epidermal membrane: Wistar rat, whole skin: Fischer 344 rat), human abdominal skin</td><td>Hydrolysis of MMA by rat liver microsomes:
V_{max} = 445.8 nmol/min/mg
K_m = 164.3 µm
Clearance = 98.8% removed from blood liver flow
T50% (body elimination time for 50% parent ester) = 4.4 min
C_{max} = 14.7 mg/L of methacrylic acid (MAA) in blood
T_{max} = 1.7 min to peak MAA concentration in blood

Hydrolysis of MMA by human liver microsomes:
V_{max} = 1721 nmol/min/mg
K_m = 4103 mM
Clearance = 419 µL/min/mg
The studies confirmed that alkyl-methacrylate esters are rapidly hydrolysed to MAA by ubiquitous carboxylesterases. First pass (local) hydrolysis of the parent ester has been shown to be significant for all routes of exposure. In vivo measurements of rat liver indicated this organ has the greatest esterase activity. Similar measurements for skin microsomes indicated approximately 20-fold lower activity than for liver. However, this activity was substantial and capable of almost complete first-pass metabolism of the alkyl-methacrylates.</td><td>Anonymous (2002)</td></tr>
<tr><td>Basic toxicokinetics in vivo (metabolism)
Non-guideline
GLP: not specified</td><td>Male Dunkin-Hartley guinea pig
2 animals per dose
Dose/concentration: 0 and 0.02 mmol/kg bw
Administration: oral, by gavage</td><td>After oral administration of the test substance, the following metabolites were identified in the urine (relative to administered dose):
Unchanged parent compound: 12 ± 1.5%</td><td>Seiss et al. (2009)</td></tr>
</table>

Method	Remarks	Results	Reference
Supporting study Reliability: 2 Test material: triethylene glycol dimethacrylate Purity: not specified (commercial grade assumed)	Vehicle: physiological saline (0.9% NaCl) Urine samples collected within 24 hours were analysed for metabolites.	Methacrylic acid (MAA): 2.4 ± 0.8% Triethylene glycol: 35 ± 2.2% Based on these data, triethylene glycol methacrylate is absorbed via the oral route and partly hydrolysed to MAA and triethylene glycol. The metabolites as well as the unchanged parent compound are excreted in urine.	
Basic toxicokinetics in vitro (metabolism) Non-guideline GLP: not specified Supporting study Reliability: 2 Test material: triethylene glycol dimethacrylate Purity: not specified (commercial grade assumed)	Objective: to identify glutathione-methacrylate adducts in erythrocytes and primary human gingival fibroblasts Dose/concentration: 0.2 mmol/L, corresponding to 572.64 mg/L based on molecular weight (286.32 g/mol) Duration: 1 hour Cell lysates and culture medium were analysed by capillary electrophoresis.	Test substance-glutathione adducts were present in the cell lysates (low intensity), and in a higher amount in the extracellular culture medium. However, no quantification was given in the publication. The test substance can form adducts with glutathione in vitro.	Nocca et al. (2011)
Dermal absorption (in silico modelling) Non-guideline Non-GLP Key study Reliability: 2 Test material: triethylene glycol dimethacrylate Purity: not specified	The physico-chemical parameters of MW, Log P and saturated aqueous solubility have been used in the evaluation of 56 methacrylate compounds. An output of predicted steady-state flux was calculated using the principles defined in the Potts and Guy prediction model (1992).	The predicted steady-state flux of the test substance is 4.989 µg/cm²/h, indicating low relative dermal absorption.	Anonymous (2013b)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

A few toxicokinetic studies are available for 2,2'-ethylenedioxydiethyl dimethacrylate and its hydrolysis product triethylene glycol, as well as for the structurally similar methyl methacrylate (MMA) (Table 8). 2,2'-ethylenedioxydiethyl dimethacrylate has a molecular weight of 286.32 g/mol and it is in liquid form at 20°C. Water solubility of the substance is 3.6 g/L at 20°C, and the octanol-water partition coefficient (log P_{OW}) is 2.30.

Absorption

The physico-chemical properties (molecular weight, physical state, water solubility, lipophilicity) of 2,2'-ethylenedioxydiethyl dimethacrylate favour absorption from the gastrointestinal tract.

The vapour pressure of a read-across substance ethyltriglycol methylacrylate is 0.077 Pa at 20°C (Anonymous 2011). This falls well below the general cut-off value of 0.5 kPa, indicating very low volatility and hence poor availability for inhalation as a vapour (ECHA 2017a). Solid particles, however, may be available for absorption after inhalation of an aerosolized substance, although this does not seem likely

considering the size of the molecule. There are no studies regarding absorption of 2,2'-ethylenedioxydiethyl dimethacrylate from the respiratory tract.

On the basis of the molecular weight, 2,2'-ethylenedioxydiethyl dimethacrylate has a relatively low ability to be absorbed through the skin. The water solubility of the substance is moderate (between 100 and 10 000 mg/L) for partitioning from the stratum corneum into the epidermis (ECHA 2017a). The predicted steady-state flux is 4.989 µg/cm²/h (Anonymous 2013b). The ester bonds of 2,2'-ethylenedioxydiethyl dimethacrylate may be hydrolysed in the skin, although to a much lesser extent than in the gastrointestinal tract due to the lower level of enzymes. The breakdown products may then be absorbed and enter the bloodstream. Proof of sensitisation after dermal contact indicates that a sufficient amount of the substance is taken up via the dermal route to induce a positive reaction in the skin (Anonymous 2014; see Section 10.7 for details).

In the absence of more specific data, absorption can be assumed to occur via oral and dermal routes. 2,2'-ethylenedioxydiethyl dimethacrylate is unlikely to be absorbed via inhalation.

Distribution

Since 2,2'-ethylenedioxydiethyl dimethacrylate is expected to undergo enzymatic hydrolysis especially in the gastrointestinal tract, the breakdown products (acid and alcohol moieties) are likely to be widely distributed due to their small size and solubility in aqueous media. The parent compound has a moderate permeability across lipid membranes (log P_{OW} 2.30), but the degradation products do not contain any lipophilic groups. The available data do not show accumulation in any organ or tissue, either. No target organs have been identified for 2,2'-ethylenedioxydiethyl dimethacrylate.

Metabolism

Ester hydrolysis is the primary step in the metabolism of methacrylate esters. In the case of diol di-methacrylate esters (such as 2,2'-ethylenedioxydiethyl dimethacrylate), one of the ester bonds is first hydrolyzed to produce the corresponding mono-ester. The second ester bond is then hydrolyzed by carboxylesterases to produce methacrylic acid (MAA) and the corresponding alcohol, triethylene glycol. 2,2'-ethylenedioxydiethyl dimethacrylate was rapidly converted to methacrylic acid in a basic toxicokinetics study conducted to investigate the in vitro hydrolysis rates (Anonymous 2013a). The hydrolysis half-lives were 3.01 minutes in rat liver microsomes and 5.68 minutes in whole rat blood. Similar metabolic pattern has been identified for a structurally similar substance, methyl methacrylate, which was hydrolyzed at a high rate to methacrylic acid, with a half-life of 4.4 minutes based on a PBPK estimation (Anonymous 2002). In the same study, the metabolism rates for alkyl-methacrylates were approximately 20 times lower in skin microsomes than in liver microsomes. Methacrylic acid will predominantly be metabolized in the liver through the valine pathway and the citric acid cycle (Cosmetic Ingredient Review 2005).

2,2'-ethylenedioxydiethyl dimethacrylate is capable of forming adducts with glutathione in vitro; low levels of these adducts have been observed in erythrocyte and gingival fibroblast cell lysates and in a higher amount in the extracellular medium (Nocca et al. 2011). Unfortunately, no quantification was provided in the study. In general, methacrylates are likely to have low reactivity with glutathione in vitro compared to the corresponding acrylates (Tanii & Hashimoto 1982, McCarthy et al. 1994). This is presumably due to steric hindrance of a nucleophilic addition at the double bond by the alpha-methyl side group. Therefore, glutathione conjugation may only play a minor role in the metabolism of alkyl and multifunctional methacrylate esters.

Excretion

The parent compound 2,2'-ethylenedioxydiethyl dimethacrylate is not likely to be excreted as such due to the rapid hydrolysis of the ester bonds. One of the main hydrolysis products, triethylene glycol, is known to be eliminated at a high degree in urine; in a rat study with radiolabelled triethylene glycol, 86-94% of the radioactivity was recovered in the urine within five days after oral administration (McKennis et al. 1961). A small but measurable amount of radioactivity was found in the faeces, and the expired air contained approximately 1% of the administered dose.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Not assessed in this dossier.

10.2 Acute toxicity - dermal route

Not assessed in this dossier.

10.3 Acute toxicity - inhalation route

Not assessed in this dossier.

10.4 Skin corrosion/irritation

Not assessed in this dossier.

10.5 Serious eye damage/eye irritation

Not assessed in this dossier.

10.6 Respiratory sensitisation

Not assessed in this dossier.

10.7 Skin sensitisation

Table 9: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, vehicle, positive control**	**Dose levels, duration of exposure**	**Results**	**Reference**
LLNA OECD TG 429 (2010) GLP Key study Reliability: 1 A pre-test was performed in 2 mice with concentrations of 50 and 100% on three consecutive days to determine the highest non-irritant test concentration.	CBA/CaOlaHsd female mice 5 per each treatment group, 5 in control group (vehicle only)	Triethylene glycol dimethacrylate (purity: 99.68%) Vehicle: acetone:olive oil (4+1 v/v), purity of the acetone 99.6% Positive control: hexyl cinnamic aldehyde (CAS 101-86-0) in acetone:olive oil (4+1 v/v)	25, 50 and 100% Induction: topical application to the dorsal surface of each ear lobe on days 1, 2 and 3 (volume: 25 µl). I.v. injection of ^{3}H-methyl thymidine via a tail vein (19.5 µCi ^{3}HTdR per mouse, volume: 250 µl) on day 6. Necropsy on day 6	**Sensitising** The SI values at 25, 50 and 100% were 1.40, 1.51 and 3.30, respectively. EC3 value: 91.6% (w/v) Observations: no mortality occurred during the study. There were no signs of systemic toxicity. The highest concentration (100%) induced slight erythema	Anonymous (2014)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, vehicle, positive control	Dose levels, duration of exposure	Results	Reference
				on the ear skin on days 3 to 6 (score 1). Animals treated with 25 and 50% of the test item did not show any signs of local skin irritation. Body weight was within normal range.	
GPMT OECD TG 406 (1981) GLP: not specified Weight of evidence Reliability: 3 A pre-test was performed to evaluate skin irritancy with 25 µL of several concentrations either injected into the flank skin or applied for 24 hours. The sites were examined after 24 and 48 hours.	Female SSc:Al outbred guinea pig 20 animals	Triethylene glycol dimethacrylate (purity not specified, but commercial grade assumed) Vehicle: soybean oil or soybean oil:2-butanone (1:2) (intradermal induction), petrolatum (topical application and challenge) Negative control: vehicle Positive control: not specified	Induction: (1) Intradermal injections (5% concentration): (i) 2 x 50 µL Freund´s complete adjuvant (FCA) and sterile water (1:1) (ii) 2 x 50 µL of test item in vehicle (iii) 2 x 50 µL of test item emulsified in FCA:water (1:1) (2) Topical application (100% concentration): A pretreatment with 250 mg 10% sodium lauryl sulphate in petrolatum On day 8, 400 µL of test substance was applied and occluded for 48 hours. Challenge: On day 21, the animals were challenged with concentrations of 25% or 100% of	**Sensitising** After 24 hours, 9/20 animals (45%) in the 25% concentration group were sensitised, and 3/20 animals (15%) in the 100% concentration group were sensitised.	Anonymous (1984a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, vehicle, positive control	Dose levels, duration of exposure	Results	Reference
			the test substance applied to the left flank.		
GPMT (modified) Non-guideline Non-GLP Weight of evidence Reliability: 3 Primary irritation evaluation: application of 0.05 ml of the test item in 1:1 acetone/dioxane containing guinea pig fat onto intact shaved skin of all 15 animals; reactions were read at 24 hours.	Male albino guinea pig 15 animals	Triethylene glycol dimethacrylate (purity: 98%) Vehicle: 1:1 acetone/dioxane containing 13% guinea pig fat (f.a.d) (animals 1-5), dimethylphthalate (DMP) (animals 6-10 and 11-15), f.a.d (challenge and rechallenge) Negative control: not specified Positive control: not specified	<u>Animals 1-5:</u> Nine topical applications (1 x 5.0%, 8 x 10%) of 0.05 ml of the test item to abraded skin <u>Animals 6-10:</u> Four intradermal injections of 1% test item <u>Animals 11-15:</u> Two 0.1 ml intradermal injections of FCA followed 1.5 hours later by a 0.1 ml of 1% test item <u>Challenge (after 2 weeks):</u> 0.05 ml of test item was applied to intact and abraded skin of all 15 animals. Because of negative results there was a rechallenge 2 weeks later, in which 0.05 ml of 25% and 100% test item was applied to flank patches. After another rest period, the animals were challenged for a third time with 0.05 ml to intact and abraded skin.	**Not sensitising** 0/15 animals were sensitised in this test; no signs of irritation were observed, either.	Anonymous (1969)
GPMT Non-guideline	Female Dunkin-Hartley guinea pig	Triethylene glycol dimethacrylate (purity min. 95%)	<u>Induction:</u> Intradermal injection with a	**Not sensitising** 1/15 animals were sensitised	Anonymous (1984b)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, vehicle, positive control	Dose levels, duration of exposure	Results	Reference
GLP: not specified Weight of evidence Reliability: 3 A pre-test was performed on three animals to determine the highest non-irritant test concentration.	15 animals	Vehicle: olive oil:acetone (9:1) (intradermal induction), petrolatum (topical induction and challenge) Negative control: vehicle Positive control: not specified	1% (w/w) concentration (ambiguity about whether adjuvant was used or not) A pretreatment with 10% (w/w) sodium lauryl sulphate in petrolatum before the topical induction Topical application with a 50% concentration <u>Challenge:</u> Intradermal injection with a 1% (w/w) concentration A challenge with hydroquinone (0.1% w/w) was also performed in all animals (no rationale or timing given).	in this test. No reactions to other acrylates or methacrylates were observed in the animal giving a positive response.	
GPMT Non-guideline Non-GLP Weight of evidence Reliability: 3 A pre-test was conducted to evaluate skin irritancy with an intradermal injection of 1% (v/v, in liquid paraffin) and a topical application of undiluted test item.	Male Dunkin-Hartley guinea pig 10 animals	Triethylene glycol dimethacrylate (purity: not specified) Vehicle: water or liquid paraffin (induction), liquid paraffin (challenge and rechallenge) Volume for intradermal injections: 0.1 ml (divided equally between left and right injection sites) Negative control: not specified Positive control: not specified	<u>Induction:</u> <u>(1) Intradermal injections:</u> (i) Freund´s complete adjuvant (FCA) diluted in water (1:1) (ii) A 1% (v/v) dilution of the test item in liquid paraffin (iii) A mixture of the test item (1% v/v in liquid paraffin) with FCA (1:1) <u>(2) Topical applications:</u> After 1 week, 0.4 ml of the undiluted test	**Not sensitising** 0/10 animals were sensitised at the dose level of 25% at none of the time points (24, 48 and 72 hours) neither after the challenge nor the rechallenge. There were no other clinical observations.	Anonymous (1973)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, vehicle, positive control	Dose levels, duration of exposure	Results	Reference
			item was applied and occluded for 48 hours. <u>Challenge:</u> Two weeks after induction, 1 ml of 25% test item (v/v) in liquid paraffin was topically applied and occluded at one flank of the animals for 24 hours. The challenge was repeated one week later at both flanks of each animal.		
GPMT Non-guideline GLP: not specified Weight of evidence Reliability: 3	Guinea pig (strain and sex not specified) 20 animals	Triethylene glycol dimethacrylate (purity: not specified) Vehicle: olive oil (both induction and challenge) Negative control: not specified Positive control: not specified	<u>Induction:</u> Intradermal injection with a 5% concentration; FCA was used as an adjuvant. Topical application with a 100% concentration <u>Challenge:</u> With 1 and 5% concentrations; administration route not specified	**Sensitising** 6/20 of the animals (30%) were sensitised in the 1% concentration group, and 15/20 of the animals (75%) were sensitised in the 5% concentration group.	Anonymous (1981)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, vehicle, positive control**	**Dose levels, duration of exposure**	**Results**	**Reference**
Polak method Non-guideline GLP: not specified Weight of evidence Reliability: 3	Hartley guinea pig, male and female No. of animals not specified 21 different acrylate and methacrylate compounds were studied for their ability to induce contact sensitivity, using 5 different sensitisation protocols.	Triethylene glycol dimethacrylate (purity not specified, but commercial grade assumed) Vehicle: ethanol:saline (1:4) in Freund´s complete adjuvant (FCA) (intradermal induction), acetone:olive oil (4:1) (open skin testing) Negative control: not specified Positive control: not specified	Intradermal injection (day 0): Concentration: 2 mg/ml Total dose (footpad and neck): 1 mg The animals received four footpad injections of 0.1 ml of an emulsion containing the test substance. 0.1 ml of the emulsion was also injected into the nape of the neck. Open skin testing (challenge, day 7): Concentration: dilutions of 5% or the maximum non-irritant concentration were used. 0.02 ml of a solution containing the test substance was applied onto the skin and repeated weekly at different sites for up to 12 weeks.	**Not sensitising** None of the animals were sensitised to the test substance (or to any other methacrylates in the test); no further information available.	Anonymous (1983)

Animal data

The sensitising potential of 2,2'-ethylenedioxydiethyl dimethacrylate has been investigated in one murine local lymph node assay and in six guinea pig studies (Table 9).

LLNA

The LLNA was conducted in accordance with OECD TG 429 (2010) and principles of GLP (Anonymous 2014). There were two deviations from the study protocol: the relative humidity in the animal room was approximately 35-45% (instead of 45-65%) for several hours, and in the pre-test the test concentration of 50% was prepared w/w (instead of w/v). Neither of these deviations is considered to affect the validity of the

study. A pre-test was performed in two mice with concentrations of 50 and 100% to determine the highest non-irritant test concentration of 2,2'-ethylenedioxydiethyl dimethacrylate. No signs of systemic toxicity was observed in the animals. On days 3 to 6, the mouse treated with 50% concentration showed an erythema of the ear skin (score 1). The mouse treated with the undiluted test substance showed an erythema of the ear skin (score 1) on days 2, 3 and 6, and on days 4 and 5 (score 2). In addition, the ears of the animal treated with 100% concentration were scabby on days 5 and 6. No excessive increases in ear weights or ear thickness values were observed.

In the main test, three treated groups of five CBA/CaOlaHsd female mice aged 8-9 weeks and weighing 18.0-22.2 g (mean 20.3 ± 1.1 g) were used. The animals were treated by topical application to the dorsal surface of left and right ears with test concentrations of 25, 50 and 100% in acetone/olive oil (4+1, v/v). The application volume, 25 µl, was spread over the entire dorsal surface (diameter ~ 8 mm) of left and right ears once daily for three consecutive days. The control group of five mice received vehicle only. Five days after the topical application, all mice were given 250 µl of 19.5 µCi ^{3}H-methyl thymidine (corresponds to 78 µCi/ml ^{3}H-methyl thymidine) by intravenous injection via the tail vein. The body weight of the animals recorded prior to the injection was within the normal range for the strain and age. All animals were euthanized approximately five hours after the injection. The left and right draining auricular lymph nodes were then excised and pooled per group. Single cell suspensions of lymph node cells were prepared from the pooled lymph nodes. The proliferative capacity of the cells was determined by the incorporation of ^{3}H-methyl thymidine measured on a β-scintillation counter.

No mortality or signs of systemic toxicity were observed during the study period. On days 3 to 6, the animals treated with the undiluted test substance showed an erythema of the ear skin (score 1). Animals treated with 25 and 50% test substance concentrations did not show any signs of local dermal irritation. The body weight of the animals remained within the normal range.

A substance is regarded as a sensitiser in the LLNA if the exposure to one or more test concentration results in a three-fold or greater increase in incorporation of ^{3}H-methyl thymidine compared with vehicle-treated controls (the ratio is termed as the Stimulation Index, SI). The estimated test substance concentration required to produce an SI is referred to as the EC3 value. In this study, Stimulation Indices of 1.40, 1.51 and 3.30 were determined at concentrations of 25, 50 and 100%, respectively (Table 10). The EC3 value was 91.6% (w/v).

Table 10: Calculation of Stimulation Indices per dose group

	Group calculation		
Test item concentration (%)	Mean DPM per animal (2 lymph nodes)[a)]	SD	SI
0 (control group)	999.4	398.8	1.00
25	1398.8	457.3	1.40
50	1510.2	457.8	1.51
100	3296.8	1256.7	3.30

DPM = disintegrations per minute, SD = standard deviation, SI = Stimulation index

[a)] = Mean DPM/animal was determined by dividing the sum of the measured values from lymph nodes of all animals within a group by the number of animals in that group (5 animals)

Guinea pig studies

The first guinea-pig study (Anonymous 1984a) was conducted using three pairs of intradermal injections of 2,2'-ethylenedioxydiethyl dimethacrylate at the induction phase. The animals were one month old at study initiation and weighed 300-350 g. A range-finding test preceded the main study; concentrations giving a definite irritation reaction on topical application were used for induction and concentrations giving no reaction were used for challenge in the main study. One intradermal injection pair in the main study

comprised Freund´s complete adjuvant (FCA) in water, the second pair the test substance (5%) in soy bean oil or soy bean oil:2-butanone, and the third pair a mixture of 5% test substance in FCA:water. Controls received the same treatment, but without the test substance. All the injection pairs were administered in the shoulder region. Prior to the topical induction exposure, there was a 24-hour pretreatment with 10% sodium lauryl sulphate in petrolatum. The actual topical induction consisted of undiluted test substance applied to the same area and occluded for 48 hours. On day 21, the animals were challenged with concentrations of 25% and 100% of the test substance applied to the left flank. The challenge sites were evaluated 48 and 72 hours after the application. 9/20 animals were sensitised in the 25% concentration group, and 3/20 were sensitised in the undiluted concentration group.

In a modified GPMT, 15 male albino guinea pigs were allocated to three groups for the induction phase of sensitisation (Anonymous 1969). Ages and weighs of the animals at study initiation are not specified in the study report. In the first group, the animals received nine topical applications (one with 5.0%, eight with 10% concentration) of 2,2'-ethylenedioxydiethyl dimethacrylate to abraded skin. The second group were given four intradermal injections of the test substance at 1% concentration, and the third group received two intradermal injections of FCA followed by an injection of the test substance at 1% concentration. After two weeks, the animals underwent the challenge phase: 2,2'-ethylenedioxydiethyl dimethacrylate (concentration not specified) was applied to intact and abraded skin of all the 15 test animals. Due to negative results, the animals were rechallenged two weeks later with 25% and 100% concentrations applied to flank patches. After another rest period, the animals were challenged for a third time with applications to intact and abraded skin; duration of the rest period or used test substance concentrations in the third challenge are not specified in the study report. None of the animals (0/15) were sensitised to 2,2'-ethylenedioxydiethyl dimethacrylate in this study.

In the third available guinea pig study, the sensitisation potential of 2,2'-ethylenedioxydiethyl dimethacrylate was examined in a GPMT, according to the method described by Magnusson and Kligman (1970) (Anonymous 1984b). The female albino guinea pigs weighed 300-400 g at the beginning of the study, but their ages are not specified. The animals received an intradermal injection of 1% test substance for induction followed by the second induction as an open topical application of 50% test substance; no further details on timing or duration are given. Prior to topical induction, 10% sodium lauryl sulphate in petrolatum was applied to the test sites. Olive oil:acetone was the vehicle used in the induction phase. The guinea pigs were challenged on day 21 with a 1% test substance in petrolatum; controls received vehicle only. 48 hours after the first challenge application, the animals were given a booster dose of the test substance applied intradermally on the neck in the same concentration and vehicle as used for the intradermal induction. The control animals received olive oil intradermally as a booster dose. There are some discrepancies in the full study report, since no use of adjuvant is mentioned in the induction phase, yet the challenge phase is reported to have been conducted otherwise in the same way as the intradermal induction phase “but without CFA”. It is also stated that a challenge with hydroquinone (0.1% w/w in alcohol) was performed in all animals, but no timing or justification for this is presented in the report. One animal (1/15) was sensitised in this study.

Ten male Dunkin-Hartley guinea pigs each received three pairs of intradermal injections at the induction phase in a non-guideline GPMT conducted according to the method described by Magnusson and Kligman (1970) (Anonymous 1973). Ages and weights of the animals at study initiation are not specified in the study report. One injection pair comprised FCA in water, the second pair a 1% injection of the test substance and the third pair a mixture of 1% test substance with FCA. All the injection pairs were administered bilaterally in the interscapular region. After one week, 2,2'-ethylenedioxydiethyl dimethacrylate was topically applied undiluted to the same area and occluded for 48 hours. Two weeks after induction, the animals were challenged with a 25% dilution of the test substance applied topically to one flank of each animal. The area was then occluded for 24 hours. The challenge was repeated one week later using the same concentration, but applying the dilution to both flanks of the animals. The challenge sites were evaluated 24, 48 and 72 hours after removal of the patch. There was no evidence of skin sensitisation in none of the animals.

In a GPMT conducted according to the Magnusson and Kligman method (1970), 20 guinea pigs were given FCA as 5% intradermal injections at the induction phase (Anonymous 1981). The strain and sex of the animals or their age or weight at study initiation are not specified in the full study report. The second induction was applied topically using a 100% concentration of 2,2'-ethylenedioxydiethyl dimethacrylate. For the challenge phase, concentrations of 1% and 5% were used. The vehicle used was olive oil for both

induction and challenge phases. There are no further details on the study design. 6/20 animals were sensitised in the 1% concentration group, and 15/20 animals were sensitised in the 5% concentration group.

21 acrylic compounds were investigated for their ability to induce skin sensitisation in male and female Hartley guinea pigs using different test protocols (Anonymous 1983). 2,2'-ethylenedioxydiethyl dimethacrylate was tested according to the non-guideline Polak method. The guinea pigs weighed 400-500 g at study initiation, but their ages are not specified in the study report. The animals (number not specified) were induced on day 0 with intradermal footpad and nape injections containing FCA in ethanol:saline. On day 7, a solution containing the test substance in acetone:olive oil was applied onto shaved flank skin. In general, dilutions of 5% or the maximum non-irritant concentration were used to test the compounds, but the study report does not specify the concentration used for 2,2'-ethylenedioxydiethyl dimethacrylate. The challenge was repeated weekly at different sites on the flank for up to 12 weeks. In this study none of the animals were sensitised to the test substance nor to any of the other acrylic compounds tested.

Human data

The most relevant clinical studies for 2,2'-ethylenedioxydiethyl dimethacrylate, 56 in total, are presented in Table 11. The studies comprised a total of 556 patients who tested positive to the substance. In all studies, the diagnostic method was patch testing. Data on skin exposure to 2,2'-ethylenedioxydiethyl dimethacrylate is scarce.

Table 11: Summary table of human data on skin sensitisation

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations** **Data on positive exposure to triethylene glycol dimethacrylate in bold**	**Reference**
CASE REPORTS ON SINGLE CASES				
Case report	Triethylene glycol dimethacrylate (2% pet.)	A 28-year-old woman with a left above-knee amputation in early childhood developed dermatitis on the stump and thigh after wearing two prostheses made of glassfibre impregnated with resin.	She tested positive to the test substance, methylmethacrylate (MMA), and the two resins used in the prostheses. Chemical analyses detected MMA, methyl polymethacrylate, and ethylene glycol dimethacrylate in both of the resins, ethyl-hexylacrylate in one of the resins and ethylhexyl methacrylate in the other resin.	Foussereau et al. (1989)
Case report	Triethylene glycol dimethacrylate (2% pet.)	A 67-year-old woman developed dermatitis on both ears and nose following the repair of her hearing aids (screwed to spectacle frames) with an acrylate resin.	On patch testing she reacted positively to 5 acrylic compounds including the test substance (+).	Dutree-Meulenberg et al. (1991)
Case report	Triethylene glycol dimethacrylate (2%	A 45-year-old female orthodontist developed	18 of 30 acrylic compounds provoked mild to strong allergic reactions in a patch test. 3	Kanerva et al. (1992)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
	in pet.)	symptoms of irritation and soreness of the throat at her workplace. There were no skin symptoms.	methacrylate-containing products were also positive on patch testing. Positive reaction to the test substance (++ on day 6).	
Case report	Triethylene glycol dimethacrylate (2%, Chemotechnique's test substance i.e. in pet.)	A 38-year-old woman was sensitised to a glue used in the attachment of car rear-view mirrors to the windscreen. She developed a dry and fissured dermatitis on fingers and palms of both hands. The dermatitis spread within a couple of weeks to lower arms, chest, neck and face.	13 acrylic compounds provoked mild to extreme allergic reactions in a patch test. Positive reaction to the test substance (+++ on days 2, 3, and 4). Triethylene glycol dimethacrylate was not mentioned in the safety data sheet of the glue or detected in chemical analysis.	Kanerva et al. (1995)
Case report	Triethylene glycol dimethacrylate (2%, vehicle not specified)	A 47-year-old atopic female cosmetician developed dermatitis on her thumb within some weeks after starting to work with photobonded nails. The dermatitis spread to both hands, and after stronger exposure to UV-gel 3 months later, she developed a severe hand and face dermatitis.	Allergic reactions to 15 (meth)acrylates, a total of 31 were tested Allergic reaction to the test substance (++). **Triethylene glycol dimethacrylate was detected in chemical analysis of the nail liquid at a concentration of 5%.**	Kanerva et al. (1996)
Case report	Triethylene glycol dimethacrylate (2% in pet.)	A 45-year-old woman presented with dermatitis of the upper and lower eyelids, which had been present intermittently for several years. She used acrylic nail overlays that	Positive reaction to the test substance (++) and to two other methacrylates. The patient removed her nail overlays, and the eyelids cleared in 3-4 days.	Guin (1998)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
		involved mixing of a liquid and powder; the application was repeated every two weeks. There were no lesions in her hands or nails.		
Case report	Triethylene glycol dimethacrylate (2% in pet.)	A 49-year-old chemist with a long history of atopic dermatitis had worked for 15 years in the development of solder-resistant inks for circuit boards. After 5 years he developed dermatitis of hands and forearms. Patch testing at that time revealed allergy to methylene bisacrylamide and ethylhexyl acrylate. He continued to work, successfully limiting exposure and with resolution of symptoms. 10 years later the eczema exacerbated, now also affecting his face.	Positive reaction to the test substance (++ on day 2, ++ on day 4). Allergic reactions also to epoxy resins, other (meth)acrylates and triglycidyl isocyanurate.	Craven et al. (1999)
Case report	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	A 37-year-old printer developed work-related hand and face dermatitis. Facial dermatitis recurred after visiting his dentist.	He tested positive to 2-hydroxymethyl methacrylate, triethylene glycol dimethacrylate, bisphenol A glyserolate dimethacrylate (bis-GMA), and his UV-cured varnish.	Bong & English (2000)
Case report	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	A 21-year-old man presented with a chronic dermatitis, with the tips of the I, II and III fingers of both hands affected by hyperkeratotic eczema.	Positive reaction to the test substance (at 48 hours + and at 72 hours +) and the two anaerobic sealants used. The material safety data sheet indicated that polyethylene glycol dimethacrylate was the principal component of one of the anaerobic	Corazza et al. (2000)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations Data on positive exposure to triethylene glycol dimethacrylate in bold	Reference
		Onycholysis was also observed in the same fingers. He had had the condition for 18 months, and his work duties included the use of anaerobic sealants. The dermatitis improved when he was away from work, and relapsed a few days after return.	sealants; the components of the other sealant could not be verified.	
Case report	Triethylene glycol dimethacrylate (2%, Chemotechnique´s substance i.e. in pet.)	A 44-year-old man presented with a 5-month history of intermittent scaling of the dorsal hands and distal phalanges, including fingertips. There had also been one episode of exudative hand dermatitis. He had started a business in replacement windows 18 months previously, affixing glass manually with a two-stage UV-cured glue.	Positive reaction to the test substance (++ on day 2, ++ on day 4). The material safety data sheet indicated that the glue contained 2-hydroxyethyl methacrylate (<50%) and ethylhexyl methacrylate (<37%). It is not clear whether accompanying reactions to other (meth)acrylates represent cross-reactivity or concomitant sensitisation.	Brooke & Beck (2002)
Case report	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	A 50-year-old beautician applied photo-bonded acrylic gel nails to customers and developed hand and forearm dermatitis.	She tested positive to the test substance, ethylene glycol dimethacrylate (EGDMA) and the acrylic nail powder that she had used.	Perale et al. (2005)
Case report	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	47-year-old woman had used acrylic nails for 10 years. She presented with periungual dermatitis of all the fingers. Symptoms had begun 6 months earlier.	She tested positive to 11 acrylic compounds including the test substance. Test substance reaction was + at 96 hours.	Paley et al. (2008)

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations** **Data on positive exposure to triethylene glycol dimethacrylate in bold**	**Reference**
Case report	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	34-year-old cosmetician developed hand eczema while applying artificial nails at work.	She had allergic reactions to 15 (meth)acrylates including the test substance (+).	Pesonen et al. (2012)
Case report	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	32-year-old manicurist developed bullous lesions on fingertips and eczema on the hands and ears. Nail products were composed of methacrylates. Her symptoms recurred when she started to work as a dental nurse.	She had allergic reactions to 7 (meth)acrylates including the test substance (++). As a dental nurse she **handled products containing triethylene glycol dimethacrylate,** 2-hydroxyethylmethacrylate, urethane dimethacrylate, and methyl methacrylate.	Kiec-Swierczynska et al. (2013)
Case report	Triethylene glycol dimethacrylate (2% in pet.)	A 28-year-old woman had had 2 episodes of acute eczematous dermatitis, first after wearing pantliners made of polyacrylate and later after varnishing of teeth with a product that contained 2-hydroxyethyl methacrylate.	She tested positive to 13 (meth)acrylates, including the test substance (+++).	Sauder et al. (2014)
PATIENT SERIES				
Patient series	Triethylene glycol dimethacrylate (1% in pet.)	6 patients (2 mechanics, 4 worked at a car assembly line) had developed contact dermatitis after using anaerobic sealants in their work.	1 patient out of 6 tested reacted positively to the test substance (16.7%). All patients reacted positively to more than one (meth)acrylate.	Condé-Salazar et al. (1988)
Patient series	Triethylene glycol dimethacrylate (2% in pet.; purity >90%)	7 patients were occupationally sensitized to methacrylate-based dental composite products.	3 patients reacted positively to the test substance out of 5 patients tested (60%). **All 5 patients tested had handled products containing triethylene glycol dimethacrylate** according to the safety data sheets.	Kanerva et al. (1989)
Patient	Triethylene glycol dimethacrylate	Report of 22 patch-tested hearing-aid	Positive reaction to the test substance in 2 (9.1%) of the	Meding & Ringdahl

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
series	(concentration and vehicle not specified)	users with severe dermatitis in the ear canal.	patients	(1992)
Patient series	Triethylene glycol dimethacrylate (1% in pet.)	Among a series of 6 patients with allergic contact dermatitis from acrylic products, a 25-year-old female dental technician presented with recurrent hand eczema, that occurred at work and subsided when she stopped working.	She tested positive to **the test substance and methacrylic acid, the two components of her DELO ML 168 glue.**	Daecke et al. (1994)
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	Report on 5 cases with severe skin symptoms in the fingers from photo-bonded acrylic nails at the Dermatologic and Pediatric Allergy Clinic in Wilhelminen Hospital, Vienna, Austria.	Positive reaction to the test substance in 4 (80%) of the patients. **Photo-bonded products contained triethylene glycol dimethacrylate,** urethane acrylates, epoxy methacrylates and hydroxyfunctional methacrylates (2-HEMA and 2-HPMA).	Hemmer et al. (1996)
Patient series	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	A retrospective study on 31 849 patients' patch test results from 24 dermatology departments included in the IVDK database in Germany in 1992-1995. Patch tests were performed in accordance with the ICDRG recommendations.	Patch test results of (meth)acrylates in dental technicians were separately reported. Positive reaction to the test substance in 7 of 137 tested dental technicians (5.1%).	Schnuch et al. (1998)
Patient series	Triethylene glycol dimethacrylate (2% in pet.), purity 98%	126 dental technicians were tested with (meth)acrylates in 1995-1999 in Department of Dermatology, Städtische Kliniken (Dortmund, DE)	Positive reaction to the test substance in 7 of 126 patients (5.6%), 6 of the reactions were assessed clinically relevant i.e. **the sensitised persons had handled test substance -containing products.** Authors considered that the sensitising potential of triethylene glycol dimethacrylate was relatively high due to low	Peiler et al. (2000)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
			frequency of skin contact in the patient material (test substance present mainly in light-curing resin systems).	
Patient series	Triethylene glycol dimethacrylate (2% and 1% in pet.)	A retrospective study of 13 833 patients tested for contact allergy at the Department of Dermatology, Catholic University (Leuven, BE) in 1978-1999 It is unclear how many patients were tested with (meth)acrylates.	72 patients were positive to some (meth)acrylate. Positive reaction to the test substance in 6 patients according to the main text of the article (there is an inconsistency between the main text and a table with 6 tetraethyleneglycol dimethacrylate reactions).	Geukens & Goossens (2001)
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	The incidence of allergic contact dermatitis was studied in 79 dentists and 46 dental nurses who were referred to the Institute of Occupational Medicine (Lodz, PL) in 1990-2000. All were tested with the European standard set, dental screening test and additional allergens.	12 dentists (15%) reacted positively to the test substance. There were no positive reactions to (meth)acrylates in dental nurses.	Kiec-Swierczynska & Krecisz (2002)
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	56 patients' charts were available for review out of 75 patients with at least one allergic reaction to meth/acrylates. 25 patients had skin symptoms from nail products and 8 were dentists or dental assistants.	7 (12.5%) patients reacted positive to the test substance.	Sood &Taylor (2003)
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	27 patients in contact with artificial nails (16 nail technicians, 11 customers) tested with acrylic	Positive reaction to the test substance in 3 (25%) of 12 patients tested with it.	Constandt et al. (2005)

<table>
<tr><th>Type of data/report</th><th>Test substance</th><th>Relevant information about the study (as applicable)</th><th>Observations

Data on positive exposure to triethylene glycol dimethacrylate in bold</th><th>Reference</th></tr>
<tr><td></td><td></td><td>compounds and apparently positive to some acrylic compound at the Departments of Dermatology in Universities of Ghent and Leuven (BE).</td><td></td><td></td></tr>
<tr><td>Patient series</td><td>Triethylene glycol dimethacrylate (2% in pet.)</td><td>90 patients suspected of having dermatitis caused by (meth)acrylates were patch tested at the Department of Occupational and Environmental Dermatology (Malmö, SE) in 1995-2004.</td><td>24 patients reacted positively to some (meth)acrylate. 10 of these patients tested positive to the test substance (41.7%).</td><td>Goon et al. (2007)</td></tr>
<tr><td>Patient series</td><td>Triethylene glycol dimethacrylate (2% in pet.)</td><td>473 patients were tested with a (meth)acrylate series at the Finnish Institute of Occupational Health (Helsinki, FI) in 1994-2006.

32 patients with allergic reaction to some (meth) acrylate and working in dental professions (dentist, dental nurse, dental technician) were identified.</td><td>Positive reactions to the test substance in 4 cases: 1 dentist (++ reaction), 2 dental nurses (++ reactions) and 1 dental technician (+ reaction).

The dental technician had handled product(s) containing the test substance according to the safety data sheet(s). The substance was commonly mentioned in safety data sheets of dentists and dental nurses.</td><td>Aalto-Korte et al. (2007)</td></tr>
<tr><td>Patient series</td><td>Triethylene glycol dimethacrylate (2% in pet.)</td><td>473 patients were tested with a (meth)acrylate series at the Finnish Institute of Occupational Health (Helsinki, FI) in 1994-2006.

Among 61 patients with allergic reaction to some (meth)acrylate, 10 patients with</td><td>Allergic reaction to the test substance in 7 (70%) of 10 patients (++ in 5 patients, +++ in 2 patients). Two patients had doubtful reactions (?+).

In 3 cases, exposure to the test substance could be confirmed:
<table><tr><th>Occupation</th><th>Reaction to test item</th><th>Conc. of test item</th></tr><tr><td>Plumber</td><td>++</td><td>10%</td></tr></table></td><td>Aalto-Korte et al. (2008)</td></tr>
</table>

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
		present occupational exposure to acrylic glues were identified.	<table><tr><td>Optician</td><td>?+</td><td>9.8%</td></tr><tr><td>Assembler of fireworks and explosives</td><td>++</td><td>15%</td></tr></table> Conc. = concentration	
Patient series	Triethylene glycol dimethacrylate (Chemotecnique's test substance, i.e. 2% pet.)	4 female patients with allergic contact dermatitis from photo-bonded acrylic gel nails. Two were customers and two were professionals wearing gel nails.	3 patients had allergic reactions to methacrylates. One patient was positive to the test substance (++). One patient was positive to triethyleneglycol diacrylate only.	Cravo et al. (2008)
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	A retrospective study on 43 patients diagnosed with allergic contact dermatitis caused by (meth)acrylates in long-lasting nail polish at dermatology departments of four Spanish hospitals in 2013-2016	Positive reaction to the test substance in 13 patients (30%).	Gatica-Ortega et al. (2017)
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	A retrospective analysis of 399 dental technicians patch tested in dermatology clinics of the IVDK network in German-speaking countries in 2001 – 2015. 226 patients with occupational contact dermatitis were included.	28 patients tested positive to the test substance among 193 tested (14.5%). 67 patients reacted to at least one (meth)acrylate.	Heratizadeh et al. (2018)
Patients series	Triethylene glycol dimethacrylate (Chemotechnique's or Trolab's test substance i.e. 2% in pet.)	A retrospective study of the European Environmental Contact Dermatitis Research Group (EECDRG) on allergic contact dermatitis from	A total of 202 patients were positive to some acrylic compound. Of these, 98 were tested with the test substance and 31 (31.6%) displayed a positive reaction to it.	Gonçalo et al. (2018)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
		(meth)acrylates due to artificial nails diagnosed in 11 clinics in 9 European countries in 2013-15		
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	A retrospective study on 16 nail technicians with methacrylate allergy who had been patch tested at the Department of Dermatology (Gävle and Malmö, SE) in 2007-2016.	Positive reaction to the test substance in 5 of 16 patients (31%).	Fisch et al. (2019)
Patient series	Triethylene glycol dimethacrylate (2% in pet.)	A retrospective study on patients suspected of nail manicure-related sensitisation to (meth)acrylates at dermatology departments of 3 Spanish hospitals in 2008-2017. A total of 208 patients were tested with (meth)acrylates.	66 patients reacted positively to at least one (meth)acrylate and the sensitisation was due to nail products. In this group, there was a positive reaction to the test substance in 19 patients (28.8%).	Marrero-Alemán et al. (2019)
Patient series	Triethylene glycol dimethacrylate (2% pet.)	2-hydroxyethyl methacrylate (HEMA) was tested in 4025 consecutive patients in 8 Italian dermatology departments between 11/2017 and 10/2018. Patients with a history suggestive to methacrylate allergy but a negative reaction to HEMA were tested with 5 additional acrylates including the test substance.	61 patients were positive to HEMA. 8 patients were tested with additional acrylates and 3 tested positive to triethylene glycol dimethacrylate.	Stingeni et al. (2019)
Patient series	Triethylene glycol dimethacrylate (2%; AllergEAZE's test	A retrospective study on 156 patch-tested patients with	51 (32.7%) patients were positive to the test substance. 116 patients had positive reactions	Gregoriou et al. (2020)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
	substance, i.e. in pet.)	a profession associated with cosmetic nail procedures or use of such services at the Department of Dermatology and Venereology, Athens, GR in 2014-2018.	to some (meth)acrylate. The test substance -positive cases constituted 44% of these.	
CROSS-SECTIONAL STUDIES ON RISK OCCUPATIONS				
Cross-sectional study	Triethylene glycol dimethacrylate (2% in pet.)	A questionnaire was sent to 1132 dental technicians and 173 answered. 55 cases were patch tested.	The test substance was positive in 2 (4%) cases of those tested (N=55). The authors stated that **the substance was commonly used in dental laboratories, and the exposure of the dental technicians could be confirmed.** They recommended that the test substance should be used more frequently instead of EGDMA, 2-HEMA and 2-HPMA due to relatively few allergic reactions compared with the other methacrylates.	Rustemeyer & Frosch (1996)
CLINICAL PATCH TEST DATA ON SELECTED PATIENTS (AIMED TESTING WITH ACRYLIC COMPOUNDS)				
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	82 patients suspected of occupational sensitisation to acrylic compounds were patch tested with the standard series and an extensive acrylate series in 1987-1992 in Italy.	One patient (1.2%), a mechanic with finger dermatitis reacted positively to the test substance and an anaerobic sealant he had used in his job. 11 patients (13.4%) reacted to some acrylic compound.	Guerra et al. (1993)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	A retrospective study on 23 patients patch tested with (meth)acrylate series at the Nofer Institute of Occupational Medicine, Lodz (PL) in 1990-1994.	Positive reactions to the test substance in 4 (17.4%) patients. Three patients were dentists and the fourth patient was a dental technician.	Kiec-Swierczynska (1996)
Patch test data, selected	Triethylene glycol dimethacrylate (2% pet.)	791 patients were tested with a denture material series in	4 patients were positive to the test substance; 2 of these were dental technicians (2/41 tested; 4.9%). In other	Gebhart & Geier (1996)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations Data on positive exposure to triethylene glycol dimethacrylate in bold	Reference
patients		1/1990−7/1993 in dermatology clinics of the IVDK network in German-speaking countries. 59 of the patients were dental technicians.	patients, the positivity ratio was 2/724 (0.3%), and in all patients 4/765 (0.5%).	
Patch test data, selected patients	Triethylene glycol dimethacrylate (2%; Chemotechnique's test substance i.e. in pet.)	A retrospective study on patients tested with (meth)acrylate patch test series at the Section of Dermatology in the Finnish Institute of Occupational Heath in 1985-1995	Positive reaction to the test substance in 23 of 275 (8.4%) patients tested with it. 48 patients reacted positively to some (meth)acrylate. The test substance -positive cases constituted 47.9% of these.	Kanerva et al. (1997)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2%; Chemotechnique´s test substance i.e. in pet.)	31 patients tested with 12 dental allergens including the test substance in Skin Department of Kasturba Medical College and Hospital in Manipal, India, in 1990−1998.	2 (6.5%) patients were positive to the test substance. One of the test substance-positive patients had mouth symptoms, orodynia and oral lichen planus.	Santosh et al. (1999)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2%, Chemotechnique's test substance i.e. in pet.)	A retrospective study of patch test records at the Section of Dermatology, University of Manchester (Salford, UK) in 1983-1998 440 patients with a history of exposure to (meth)acrylates were patch tested with (meth)acrylates.	Positive reaction to the test substance in 21 of 343 patients (6.1%) tested with it.	Tucker & Beck (1999)
Patch test data, selected patients	Triethylene glycol dimethacrylate (concentration or vehicle not specified)	A retrospective study on patients patch tested with dental screening series in 7 dermatology clinics in Finland in 1994-1998.	There were 12 (0.5%) allergic reactions to the test substance in the 2586 patients tested. The frequency of allergic reactions varied between 0.0% and 2.9% in different clinics.	Kanerva et al. (2001)

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations** **Data on positive exposure to triethylene glycol dimethacrylate in bold**	**Reference**
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	109 patients (all dental personnel) were tested with a dental screening series at the Department of Occupational and Environmental Dermatology (Stockholm, SE) in 1995-1998.	Positive reaction to the test substance in 7% (8) of 109 patients tested with (meth)acrylates. 3 were dentists and 5 dental nurses. 24 patients had allergic reactions to some (meth)acrylate. The 8 test substance -positive cases constituted 33% of these.	Wrangsjö et al. (2001)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	325 dermatitis patients were patch tested for sensitivity to 21 dental metals and 334 dermatitis patients for sensitivity to 11 dental materials in 1996-2000 at the Department of Dermatology in Omori Hospital in Tokyo, Japan.	0.8% of the 334 patients were sensitised to the test substance (non-occupational exposure). Number of sensitised patients was possibly 3. No further information available (article in Japanese, data extracted from abstract in English)	Washizaki (2003)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	A retrospective study of patch test records of 1632 patients tested with dental patient and/or dental personnel series at the Department of Occupational and Environmental Dermatology in Malmö University Central Hospital (SE) in 1995-2004.	Positive reaction to the test substance in 13 (0.8%) of 1632 patients tested. 48 patients reacted positively to at least one (meth)acrylate. The test substance -positive cases constituted 27% of these.	Goon et al. (2006)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2%; Chemotechnique's test substance, i.e. in pet.)	55 patients with hand dermatitis and contact with artificial nails were tested with 'methacrylate artificial nail series' in 2001−2004 in Dermatology Clinic, in Meir Hospital, Tel Aviv, Israel.	8 (14.5%) patients were positive to the test substance. 4 patients were occupational cases (beauticians/nail artists) and 4 patients were consumers of nail products.	Lazarov (2006)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations Data on positive exposure to triethylene glycol dimethacrylate in bold	Reference
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	A retrospective study on 451 patients suspected of having occupational contact dermatitis and tested with a (meth)acrylate series at the Finnish Institute of Occupational Health (Helsinki, FI) in 1994-2009.	Positive reaction to the test substance in 15 patients (3.3%) 66 patients reacted positively to at least one (meth)acrylate. The test substance -positive cases constituted 22.7% of this group.	Aalto-Korte et al. (2010) Includes the patients in Aalto-Korte et al. (2007) and Aalto-Korte et al. (2008)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2%; Chemotechnique's test substance i.e. in pet.)	A retrospective study on patients tested with (meth)acrylate series at the Department of Dermatology, University Medical Centre in Groningen (NL) in 1993-2012	Positive reactions in 6 (4.0%) of 151 patients tested with the test substance. 24 patients reacted positively to some (meth)acrylate. The positive reactions to triethylene glycol dimethacrylate constituted 25% of these.	Christoffers et al. (2013)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	122 patients were tested with an extended series of (meth)acrylates at the Department of Dermatology (Coimbra, PT) in 2006-2013	Positive reaction to the test substance in 7 (5.7%) patients. 37 patients reacted positively to (meth)acrylates. The test substance -positive cases constituted 18.9% of these.	Ramos et al. (2014)
Patch test data, selected patients	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	72 244 female patients were retrospectively analysed for allergic reactions to (meth)acrylates. The patients had been patch-tested in 2004−2013 in dermatology departments of the IVDK network in German-speaking countries.	120 patients were positive to the test substance among 8731 tested (1.4%). 14 of the 120 patients were nail artists or beauticians.	Uter & Geier (2015)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2% in pet.)	475 patients were tested with a (meth)acrylate series at the Cutaneous Allergy Unit (Birmingham,	Positive reactions to the test substance in 17 (3.6%) patients tested. 52 patients reacted positively to (meth)acrylates. The patients with positive reactions to triethylene	Spencer et al. (2016)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations **Data on positive exposure to triethylene glycol dimethacrylate in bold**	Reference
		UK) in 2002-2015.	glycol dimethacrylate constituted 33% of these.	
Patch test data, selected patients	Triethylene glycol dimethacrylate (Chemotechnique´s test substance i.e. 2%, in pet.)	Retrospective analysis of patch data on 18 195 consecutive patients in 9 dermatology centres in the UK in 2008−2015. Of these, 1306 selected patients were tested with (meth)acrylates.	37 patients had allergic reactions to the test substance, 2.8% of patients were tested with the test substance. (0.2% of all the patch tested patients during the same time period)	Rolls et al. (2018)
Patch test data, selected patients	Triethylene glycol dimethacrylate (2%, vehicle not stated; FIRMA Diagent allergen)	A prospective study on screening contact allergy to acrylic acid on 436 consecutively patch-tested patients in 3 Italian patch test clinics in January − March 2018. Additional patch tests with (meth)acrylate series were performed in patients positive to acrylic acid or 2-hydroxyethyl methacrylate or with a history of (meth)acrylate allergy.	30 patients were tested with (meth)acrylates including the test substance. Positive reaction to the test substance in 2 patients (6.7% of those tested). **One of the allergic reactions was considered relevant as triethylene glycol dimethacrylate was listed in the safety data sheets of the products.** The other reaction was considered a cross-reaction to acrylic acid.	Hansel et al. (2020)

Recording of patch test reactions: + (weak positive reaction; erythema, infiltration, possibly papules), ++ (strong positive reaction; erythema, infiltration, papules, vesicles), +++ (extreme positive reaction; intense erythema, infiltrate, coalescing vesicles), ?+ (doubtful reaction; faint erythema only) (Johansen et al. 2015)

Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and is performed according to international standards by dermatologists (Johansen et al. 2015). The results of such tests are usually reported as number of patients/subjects with positive reactions in relation to the total number of tested (frequency of positive patch tests). An important factor of assessing prevalence of positive reactions in diagnostic patch test is how the group of patients is defined, i.e. if they are selected some way or not. Selected patients can be, for instance, patients with dermatitis suspected of having contact with acrylic compounds or special occupational groups (aimed testing). Consecutive or unselected patients are groups of patients for whom allergic contact dermatitis is generally suspected.

There are no studies on diagnostic patch tests with 2,2'-ethylenedioxydiethyl dimethacrylate in general population or unselected clinical patients.

2,2'-ethylenedioxydiethyl dimethacrylate is usually tested as part of (meth)acrylate patch test series, and its established test concentration is 2% in petrolatum. A total of 18 diagnostic patch test studies on selected patients could be identified for the substance. The frequency of positive reactions varied between 0.5% and 17.4% (median 3.5%).

No strict workplace studies could be identified for 2,2'-ethylenedioxydiethyl dimethacrylate. However, one cross-sectional study on dental technicians, who are at risk of developing a contact allergy due to exposure to acrylic compounds at work, shares a similar design. Only the workers with skin symptoms were patch tested in this study. Frequency of positive reactions to the substance was 4% (2 of 55 patients tested; Rustemeyer & Frosch 1996).

The rest of the identified studies were either case reports of single cases (n=15) or reports describing patient series (n=22) without clearly stating the frequency of a positive reaction in all patients tested with the substance during the same time period. In the majority of the clinical reports, specific exposure to 2,2'-ethylenedioxydiethyl dimethacrylate in patch-tested patients, or those who tested positive to the substance, is not verified. However, in ten studies comprising a total of 23 cases positive to 2,2'-ethylenedioxydiethyl dimethacrylate the use of products containing the substance could be confirmed. Of these, four were reports of single cases (Daecke et al. 1994, Kanerva et al. 1996, Aalto-Korte et al. 2007, Kiec-Swierczynska et al. 2013). In addition, Hansel et al. (2020) describe confimed exposure in one of two patients who reacted positively to 2,2'-ethylenedioxydiethyl dimethacrylate. In the rest of the studies there were two (Rustemeyer and Frosch 1996), three (Kanerva et al. 1989, Aalto-Korte et al. 2008), four (Hemmer et al. 1996) and six (Peiler et al. 2000) patients with confirmed exposure to products containing 2,2'-ethylenedioxydiethyl dimethacrylate. In four of the 23 positive cases, concentrations of the substance could be verified based on chemical analysis of acrylic glues used (5% in the Kanerva et al. 1996 study, 9.8%, 10% and 15% in the Aalto-Korte et al. 2008 study).

Table 12: Summary table of other studies relevant for skin sensitisation

No other studies are available.

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Animal data

In the OECD- and GLP-compliant LLNA, three treated groups of five mice were administered 2,2'-ethylenedioxydiethyl dimethacrylate topically at concentrations of 25, 50 and 100% in acetone/olive oil (4+1, v/v) (Anonymous 2014). The control group of five mice received vehicle only. No mortality or signs of systemic toxicity were observed during the study period. On days 3 to 6, the animals treated with the undiluted test substance showed an erythema of the ear skin (score 1). Animals treated with 25 and 50% test substance concentrations did not show any signs of local dermal irritation. A clear dose-response in the stimulation index (SI) values was not observed. The threshold positive value of 3 was exceeded at 100% concentration, and the EC3 value was 91.6% (w/v).

Six guinea pig studies from the 1960s-1980s are also available for the evaluation of skin sensitisation potential of 2,2'-ethylenedioxydiethyl dimethacrylate. Only one of them, the Anonymous 1984a, complies with the OECD test guideline (TG 406, 1981), although with deviations (purity of the substance not known, positive control not specified). The majority of the remaining studies are modified GPMTs, except the Anonymous 1983, which was conducted using the Polak method. 2,2'-ethylenedioxydiethyl dimethacrylate was found to be a sensitiser in two of the GPMTs (6/20 and 15/20 sensitised animals in the Anonymous 1981 study, 9/20 and 3/20 sensitised animals in the Anonymous 1984a study), whereas the remaining three GPMTs gave negative results (0/15 animals were sensitised in the Anonymous 1969, 0/10 in the Anonymous 1973, and 1/15 in the Anonymous 1984b studies). However, both the studies giving a positive response have their deviations; apart from the unspecified purity of the substance and positive control, the Anonymous 1981 study also lacks information on strain and sex of the tested animals. Moreover, the positive results were obtained with intradermal induction concentrations of 5%, and all the negative results with concentrations of

1%. None of the guinea pigs were sensitised in the Polak test, yet the number of animals tested is not specified in the study report (Anonymous 1983).

Human data

A total of 56 clinical studies have been identified for 2,2'-ethylenedioxydiethyl dimethacrylate. There are no studies in general population or unselected clinical patients. 2,2'-ethylenedioxydiethyl dimethacrylate is usually tested as part of the (meth)acrylate patch test series, and a total of 18 diagnostic patch test studies on selected patients could be identified for the substance. The frequency of positive reactions varied between 0.5% and 17.4% (median 3.5%) in the studies.

There are no strict workplace studies for 2,2'-ethylenedioxydiethyl dimethacrylate. In the only available cross-sectional risk occupation study (mimicking a workplace study), dental technicians were patch tested with the substance (Rustemeyer & Frosch 1996). Only the workers with skin symptoms were tested in the study. Frequency of positive reactions to the substance was 4% (2 of 55 patients tested).

The rest of the identified studies were either case reports of single cases (n=15) or reports describing patient series (n=22) without clearly stating the frequency of a positive reaction in all patients tested with the substance during the same time period. In the majority of the clinical reports, specific exposure to 2,2'-ethylenedioxydiethyl dimethacrylate in patch-tested patients, or those who tested positive to the substance, is not verified. However, in ten studies comprising a total of 23 cases positive to 2,2'-ethylenedioxydiethyl dimethacrylate the use of products containing the substance could be confirmed. In four of these 23 cases, the concentrations of 2,2'-ethylenedioxydiethyl dimethacrylate were 5%, 9.8%, 10% and 15% based on chemical analysis of the acrylic glues used (Kanerva et al. 1996, Aalto-Korte et al. 2008).

10.7.2 Comparison with the CLP criteria

Substances are classified as Category 1 skin sensitisers where data are not sufficient for sub-categorisation, if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or if there are positive results from an appropriate animal test (Annex I, Table 3.4.2 of the CLP Regulation).

Substances are classified as Sub-category 1A skin sensitisers where there is evidence of a high frequency of occurrence in humans and/or a high potency in animals. Such evidence includes

> Human evidence: diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure.
>
> GPMT: ≥30% responding at ≤0.1% intradermal induction dose or ≥60% responding at >0.1% to ≤1% intradermal induction dose.
>
> LLNA: EC3 value ≤2%.

Substances are classified as Sub-category 1B skin sensitisers where there is evidence of a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals. Such evidence includes:

> Human evidence: diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure.
>
> GPMT: ≥30% to <60% responding at >0.1% to ≤1% intradermal induction dose or ≥30% responding at >1% intradermal induction dose.
>
> LLNA: EC3 value >2%.

In the key LLNA (conducted in compliance with OECD TG 429 and GLP), 2,2'-ethylenedioxydiethyl dimethacrylate showed an EC3 value of 91.6% (w/v), indicating a low to moderate skin sensitisation potency. According to the Guidance on the Application of the CLP Criteria (ECHA 2017b, Table 3.4.4), the result would allow classification in Skin Sens. 1B, and exclude classification in Skin Sens. 1A. Six guinea pig tests from the 1960s-1980s are also available for assessment; of these studies, two GPMTs (Anonymous 1984a, 1981) gave positive results with ≥30% of the animals responding at >1% intradermal induction dose. In the Anonymous 1984a study, a 5% intradermal induction dose led to sensitisation of 45% and 15% of the animals, whereas in the Anonymous 1981 study the same dose led to sensitisation of 30% and 75% of the

animals. However, due to the methodological limitations of these studies and higher concentrations used for intradermal induction compared to the studies giving a negative response, the reliability of the positive results is rather questionable. They are, nevertheless, in line with the LLNA, according to which 2,2'-ethylenedioxydiethyl dimethacrylate is a weak sensitiser. Based on these two positive studies, classification in Sub-category 1A cannot be reliably excluded as lower intradermal induction concentrations were not tested. Subcategorisation is, however, justified based on the key LLNA, hence classification as Skin Sens. 1B is warranted.

Human data

According to the classification criteria human evidence for Sub-categories 1A and 1B, respectively, can include the following type of data (ECHA 2017b, Section 3.4.2.2.3.1.):

	Human data
Sub-category 1A	(a) positive responses at ≤ 500 µg/cm2 (HRIPT, HMT – induction threshold); (b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure; (c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.
Sub-category 1B	(a) positive responses at > 500 µg/cm2 (HRIPT, HMT – induction threshold); (b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure; (c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

HRIPT: Human Repeat Insult Patch Test; HMT: Human Maximisation Test

The Guidance on the Application of the CLP Criteria further outlines how high or low frequency of occurrence of skin sensitisation shall be assessed (ECHA 2017b, Section 3.4.2.2.3.1., Table 3.2):

Human diagnostic patch test data	**High frequency**	**Low/moderate frequency**	**2,2'-ethylenedioxydiethyl dimethacrylate**
General population studies	≥ 0.2 %	< 0.2 %	No studies
Dermatitis patients (unselected, consecutive)	≥ 1.0 %	< 1.0 %	No studies
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0 %	< 2.0 %	18 studies: 0.5%-17.4% (median 3.5%)
Workplace studies: 1: all or randomly selected workers 2: selected workers with known exposure or dermatitis	 ≥ 0.4 % ≥ 1.0 %	 < 0.4 % < 1.0 %	 No studies 1 study: 4%
Number of published cases	≥ 100 cases	< 100 cases	556 patch-test-

			positive cases

There are no studies on general population or on unselected consecutive dermatitis patients.

Frequencies of positive patch tests in 18 selected dermatitis patient materials (aimed testing) have been mostly above the limit of high frequency (0.5%-17.4%; median 3.5%)

In the only available cross-sectional study on a risk occupation (mimicking a workplace study), the frequency of positive patch tests was 4%, i.e. above the cut-off value of 1.0%. Not all or randomly selected workers but those with skin symptoms were patch tested in this study. The authors stated that all dental technicians in this study were exposed to 2,2'-ethylenedioxydiethyl dimethacrylate.

The number of published patch-test-positive cases, 556, exceeds the limit for high frequency.

Positive patch test reactions to 2,2'-ethylenedioxydiethyl dimethacrylate are quite common in patients sensitised to methacrylates, but specific exposure to the substance in sensitised patients or patients tested was described only in 10 studies of the 56 studies reviewed. These 10 studies comprised a total of 23 individuals with an allergic reaction to 2,2'-ethylenedioxydiethyl dimethacrylate and exposure to products containing the substance. Both the exposure and the lack of exposure to 2,2'-ethylenedioxydiethyl dimethacrylate are typically difficult to assess in clinical work due to the unavailability of chemical analyses. However, in four of the 23 positive cases, concentrations of 2,2'-ethylenedioxydiethyl dimethacrylate in the used products could be analytically confirmed (5% in the Kanerva et al. 1996 study and 9.8%, 10% and 15% in the Aalto-Korte et al. 2008 study). All these four cases were occupational, which raises the probability of repeated exposure. Positive reactions may also arise from cross-reactivity to other methacrylates, yet true exposure to 2,2'-ethylenedioxydiethyl dimethacrylate in clinical patients cannot be excluded.

To conclude, the frequency of positive reactions to 2,2'-ethylenedioxydiethyl dimethacrylate in diagnostic patch tests can be considered high. However, there is no adequate information enabling the assessment of true exposure to the substance. Human data supports the classification of 2,2'-ethylenedioxydiethyl dimethacrylate as a skin sensitiser.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the available data, the proposed classification and labelling for skin sensitisation is **Skin Sens. 1B**. The corresponding hazard statement is **H317: May cause an allergic skin reaction**. There is no adequate and reliable scientific information available to set a specific concentration limit for the substance.

10.8 Germ cell mutagenicity

Not assessed in this dossier.

10.9 Carcinogenicity

Not assessed in this dossier.

10.10 Reproductive toxicity

Not assessed in this dossier.

10.11 Specific target organ toxicity-single exposure

Not assessed in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Not assessed in this dossier.

10.13 Aspiration hazard

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Not assessed in this dossier.

11.2 Environmental transformation of metals or inorganic metals compounds

Not assessed in this dossier.

11.3 Environmental fate and other relevant information

Not assessed in this dossier.

11.4 Bioaccumulation

Not assessed in this dossier.

11.5 Acute aquatic hazard

Not assessed in this dossier.

11.6 Long-term aquatic hazard

Not assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Not assessed in this dossier.

13 ADDITIONAL LABELLING

The label on the packaging of mixtures not classified as sensitising but containing 2,2'-ethylenedioxydiethyl dimethacrylate, classified as Skin Sens. 1B; H317, in a concentration of ≥ 0,1% shall bare the statement EUH208 (CLP Annex II, Section 2.8).

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15 ANNEXES

None