Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2,2'-ethylenedioxydiethyl dimethacrylate

EC Number: 203-652-6
CAS Number: 109-16-0

CLH-O-0000007059-70-01/F

Adopted

26 November 2021

26 November 2021

CLH-O-0000007059-70-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **2,2'-ethylenedioxydiethyl dimethacrylate**

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

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

The proposal was submitted by **Finland** and received by RAC on **11 November 2020.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Finland has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **7 December 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **5 February 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **26 November 2021** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 Annex VI entry										
Dossier submitters proposal	-	2,2'-ethylenedioxydiethyl dimethacrylate	203-652-6	109-16-0	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-
RAC opinion	-	2,2'-ethylenedioxydiethyl dimethacrylate	203-652-6	109-16-0	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-
Resulting Annex VI entry if agreed by COM	-	2,2'-ethylenedioxydiethyl dimethacrylate	203-652-6	109-16-0	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) provided human data on skin sensitisation and results of 5 animal studies to assess the skin sensitising property of 2,2'-ethylenedioxydiethyl dimethacrylate: one murine local lymph node assay (LLNA) and four guinea pig maximisation testes (GPMT).

Animal studies

1. The **LLNA** was conducted in accordance with OECD TG 429 (2010) and principles of GLP (Anonymous 2014) and is considered reliable and a key study by the Dossier Submitter. In the pre-test, no signs of systemic toxicity were observed in the animals, but slight erythema of the ear skin (score 1) was observed in treated mice after application of 2,2'-ethylenedioxydiethyl dimethacrylate at concentrations of 50% and 100%.The intensity of skin erythema in mice treated with undiluted substance increased to score 2 on days 4 and 5. 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 control group of five mice received vehicle only. Five days after the topical application, all mice were given 250 µl of 19.5 µCi 3H-methyl thymidine (corresponds to 78 µCi/ml 3H-methyl thymidine) by intravenous injection via the tail vein. The proliferative capacity of the cells was determined by the incorporation of 3H-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 test substance at concentrations of 25 and 50% did not show any signs of local dermal irritation. The body weight of the animals remained within the normal range.

In this study, Stimulation Indices (SI) of 1.40, 1.51 and 3.30 were determined at concentrations of 25, 50 and 100%, respectively and EC3 value was 91.6% (w/v). It is noted that only undiluted substance was a skin sensitiser, while lower concentrations (with 25 and 50%) did not induce a response, which could indicate low skin sensitising potency.

2. The first **guinea-pig study** (Anonymous 1984a) was conducted according to OECD TG 406, but GLP conditions were not confirmed. The DS has assigned to this study a reliability index of 3. Purity of the test substance was not specified, but commercial grade was assumed. The concentrations giving a definite irritation reaction on application in a range-finding test were used in the main study for induction (concentration of 5% for intradermal injections) while the concentrations giving no reaction after topical application in a range-finding test were used for challenge in the main study (25% or 100% of a test substance). In the challenge test 9/20 animals (45%) in the 25% concentration group were sensitised, and 3/20 animals (15%) in the 100% concentration group were sensitised. It is noted that no dose-response was observed with increase of concentration in the challenge test, and only the incidence of sensitised animals (45%)

which were challenged with 25% concentration of the test substance was above the criterion for sub-category 1B: ⩾ 30 % responding animals at > 1 % intradermal induction dose in the GPMT. The incidence of sensitised guinea pigs (15%) challenged with undiluted test substance was below that criterion.

3. In a modified GPMT (Reliability 3) 15 male albino guinea pigs were allocated to three groups for the induction phase of sensitisation (Anonymous 1969). 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 was given four intradermal injections of the test substance at 1% concentration, and the third group received two intradermal injections of FCA (Freund's Complete Adjuvant) 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 the third time with applications to intact and abraded skin; duration of the rest period or used test substance concentrations in the third challenge were not specified in the study report. None of the animals (0/15) were sensitised to 2,2'-ethylenedioxydiethyl dimethacrylate in this study.

4. In the third GPMT (Reliability 3) (Anonymous 1984b), the sensitisation potential of 2,2'-ethylenedioxydiethyl dimethacrylate was examined in a GPMT, according to the method described by Magnusson and Kligman (1970). The female albino guinea pigs 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 FCA". One animal (1/15, 6.6%) was reported to be sensitised in this study.

5. In the fourth GPMT (Reliability 3) (Anonymous 1973) 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). 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 any of the animals.

6. The fifth GPMT (Reliability 3) (Anonymous 1981) was conducted according to the Magnusson and Kligman method (1970). Twenty guinea pigs were given FCA as 5% intradermal injections

at the induction phase. The second induction was applied topically using a 100% concentration of 2,2'-ethylenedioxy diethyl 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. In the challenge phase 6/20 animals (30%) were sensitised in the 1% concentration group, and 15/20 animals (75%) were sensitised in the 5% concentration group.

7. In the sixth GPMT (Reliability 3), 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 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 1. 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.

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**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	On patch testing she reacted positively to 5 acrylic compounds including the test substance (+).	Dutree-Meulenberg *et al.* (1991)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		aids (screwed to spectacle frames) with an acrylate resin.		
Case report	Triethylene glycol dimethacrylate (2% in pet.)	A 45-year-old female orthodontist developed symptoms of irritation and soreness of the throat at her workplace. There were no skin symptoms.	18 of 30 acrylic compounds provoked mild to strong allergic reactions in a patch test. 3 methacrylate-containing products were also positive on patch testing. Positive reaction to the test substance (++ on day 6).	Kanerva *et al.* (1992)
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	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)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		after stronger exposure to UV-gel 3 months later, she developed a severe hand and face dermatitis.		
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 involved mixing of a liquid and powder; the application was repeated every two weeks. There were no lesions in her hands or nails.	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)
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	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)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		continued to work, successfully limiting exposure and with resolution of symptoms. 10 years later the eczema exacerbated, now also affecting his face.		
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. 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	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 sealants; the components of the other sealant could not be verified.	Corazza *et al.* (2000)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		days after return.		
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	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)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
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 series	Triethylene glycol dimethacrylate (concentration and vehicle not specified)	Report of 22 patch-tested hearing-aid users with severe dermatitis in the ear canal.	Positive reaction to the test substance in 2 (9.1%) of the patients	Meding & Ringdahl (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 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	A retrospective study on 31 849 patients' patch test	Patch test results of (meth)acrylates in dental technicians were separately reported.	Schnuch *et al.* (1998)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
	and vehicle not specified)	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.	Positive reaction to the test substance in 7 of 137 tested dental technicians (5.1%).	
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 frequency of skin contact in the patient material (test substance present mainly in light-curing resin systems).	Peiler *et al.* (2000)
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	12 dentists (15%) reacted positively to the test substance. There were no positive reactions to (meth)acrylates in dental nurses.	Kiec-Swierczynska & Krecisz (2002)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		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.		
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 compounds and apparently positive to some acrylic compound at the Departments of Dermatology in Universities of Ghent and Leuven (BE).	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</th><th>Reference</th></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 provided to 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</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><td>Occupation</td><td>Reaction to test item</td><td>Concentration of test item</td></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	Reference
		(meth)acrylate, 10 patients with present occupational exposure to acrylic glues were identified.	Optician ?+ 9.8% Assembler of fireworks and explosives ++ 15%	
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)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
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 (meth)acrylates due to artificial nails diagnosed in 11 clinics in 9 European countries in 2013-15	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)
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)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
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 substance, i.e. in pet.)	A retrospective study on 156 patch-tested patients with a profession associated with cosmetic nail procedures or use of such services at the Department of Dermatology and Venereology, Athens, GR in 2014-2018.	51 (32.7%) patients were positive to the test substance. 116 patients had positive reactions to some (meth)acrylate. The test substance -positive cases constituted 44% of these	Gregoriou *et al.* (2020)
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	Rustemeyer & Frosch

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			EGDMA, 2-HEMA and 2-HPMA due to relatively few allergic reactions compared with the other methacrylates.	
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 patients	Triethylene glycol dimethacrylate (2% pet.)	791 patients were tested with a denture material series in 1/1990 - 7/1993 in dermatology clinics of the IVDK network in German-speaking countries. 59 of the patients were dental technicians.	4 patients were positive to the test substance; 2 of these were dental technicians (2/41 tested; 4.9%). In other patients, the positivity ratio was 2/724 (0.3%), and in all patients 4/765 (0.5%).	Gebhart & Geier (1996)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
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)acrylate s were patch tested with (meth)acrylates.	Positive reaction to the test substance in 21 of 343 patients (6.1%) tested.	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	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)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
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)
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	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)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		Department of Dermatology (Coimbra, PT) in 2006-2013		
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, UK) in 2002-2015.	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 glycol dimethacrylate constituted 33% of these.	Spencer *et al.* (2016)
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	A prospective study on screening contact allergy	30 patients were tested with (meth)acrylates including the test substance.	Hansel *et al.* (2020)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
	stated; FIRMA Diagent allergen)	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.	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.	

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)

Selected patients are 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 study 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 was not verified in patch-tested patients or in those who tested positive to the substance. 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 confirmed 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).

Comments received during consultation

One MSCA supported proposed classification of the 2,2'-ethylenedioxydiethyl dimethacrylate as Skin Sens 1B, H317. The argumentation that the human patch-test data suggest at least a categorization as skin sensitiser with high frequency is plausible. Finally, the key-LLNA clearly confirms the subcategorization as Skin Sens 1B, H317.

Another MSCA noted that based on results of the LLNA, criteria for Skin Sens. 1B are fulfilled. The EC3 value is however 91.6%, indicating a low potency. Based on human data and according to CLP guidance document, there is a high frequency of occurrence of skin sensitisation based on the available studies on selected patients (in general > 2%) and the high number of published cases (> 100). Assessment of exposure data is lacking from the CLH report (refer to table 3.3 of CLP guidance). Considering the high frequency of occurrence of skin sensitisation based on human data, if no adequate exposure data are available, a subcategorisation as Skin Sens. 1A cannot be excluded. In this context, subcategorisation may not be possible. Thus, it should be discussed at the RAC level if classification as Skin Sens. 1 instead of 1B as proposed is more appropriate.

In response, the DS pointed out that the assessment of human exposure is not included in the CLH report because there is no adequate data available. Proposed sub-categorization as 1B is based on reliable LLNA. In this case, the DS view is that insufficient human exposure data would not overtake animal data. However, the DS agreed that it is the RAC to consider the most appropriate classification.

One Company-Importer agreed with the harmonised classification as Skin Sens 1B, H317, mainly based on animal data, namely LLNA data, proposed by the Finnish MSCA. They also agreed to the proposed assessment on human data supporting the classification and labelling in a weight of evidence approach and not allowing a sub-categorisation due to the absence of exposure information.

Assessment and comparison with the classification criteria

According to Regulation (EC) 1272/2008, point 3.4.2.2.4.2.: "*Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on skin sensitisation are usually derived from case-control or other, less defined studies.*

Evaluation of human data must therefore be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken."

In the case of 2,2'-ethylenedioxydiethyl dimethacrylate both human data and animal data were provided.

Animal data

Results of 7 animal studies are available: one murine LLNA and six GPMT. The LLNA (Anonymous 2014) has been assessed with reliability index 1 and used by DS as a key study.

In the current Guidance on the Application of CLP Criteria (point 3.4.2.2.2) it is noted that classification into sub-categories is only possible if there are sufficient data. Therefore, it is not appropriate to classify substances into category 1B when category 1A cannot be excluded. In such cases classification into category 1 should be considered.

In order to classify a substance into sub-category 1A in the LLNA, a value of EC3 should be ≤ 2 % while that for the subcategory 1B should be > 2 %. Therefore, in order to classify in sub-category 1B (if the EC3 is > 2 %), there is also a need for data demonstrating that a substance at a concentration of ≤ 2 % will not induce an SI ≥ 3 and is therefore not meeting the CLP criteria for sub-category 1A. The results of LLNA (Anonymous, 2014) indicate that 2,2'-ethylenedioxydiethyl dimethacrylate did not induce a stimulation index above 3 at concentration of 25% and 50%, therefore it will not induce such an index at a concentration 10 times lower. Consequently, classification of this substance to category 1A can be excluded and subcategorization is possible. 2,2'-ethylenedioxydiethyl dimethacrylate has induced in LLNA the stimulation index above 3 at concentration of 100%, with EC3 calculated to be 91.6%, meeting classification criteria for category 1B. Since classification to subcategory 1A can be excluded, it warrants, based on results of LLNA, classification to category 1B.

Only two out of six skin sensitisation studies on guinea pigs (Anonymous, 1981; Anonymous, 1984a) with reliability index 3 were positive. In the first positive study (Anonymous, 1984a) 45% of animals (9/20 animals) responded with skin reaction when the concentration of 2,2'-ethylenedioxydiethyl dimethacrylate in the challenge test was 25%, and 15% (3/20 animals) have positive response when concentration of the test substance in the challenge test was 100%. Since in this study (Anonymous, 1984a) concentration of the test substance for intradermal induction was 1%, the 45% of sensitised guinea pigs meet criteria for classification to sub-category 1B (≥ 30 % to < 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose, Table 3.4.4 of Regulation 1272/2008). In the second positive study (Anonymous, 1981) the percentage of sensitised animals after intradermal induction with 2,2'-ethylenedioxydiethyl dimethacrylate at concentration of 5% was 30% and 75% depending upon the concentration used in the challenge test (1% and 5%, respectively) (Anonymous, 1981). Such incidences (30% and 75%) meet the classification criteria for subcategory 1B (incidence ⩾ 30 % responding at > 1 % intradermal induction dose, Table 3.4.4 of Regulation 1272/2008). It is noted that lower concentrations for intradermal induction were not tested, therefore neither study (Anonymous, 1984a; Anonymous, 1981) provide sufficient evidence for subcategorization, because subcategory 1A cannot be excluded. However, they create a supportive evidence of skin sensitisation of guinea pigs to 2,2'-ethylenedioxydiethyl dimethacrylate. Four negative studies of skin sensitisation of 2,2'-ethylenedioxydiethyl dimethacrylate on guinea pigs seem to indicate a low sensitising potency of this substance (Anonymous, 1969; Anonymous, 1973; Anonymous, 1983; Anonymous, 1984b), although their reliability is low.

Human data

According to the classification criteria listed in points 3.4.2.2.2.1 and 3.4.2.2.2.2 of Regulation (EC) 1272/2008 the 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	(d) positive responses at > 500 µg/cm2 (HRIPT, HMT – induction threshold); (e) 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; (f) 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), results provided for 2,2'-ethylenedioxydiethyl dimethacrylate:

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	≥ 0.4 %	< 0.4 %	No studies
2: selected workers with known exposure or dermatitis	≥ 1.0 %	< 1.0 %	1 studies: 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 studies (aimed testing) have been mostly above (≥ 2.0 %) the limit of high frequency (0.5%-17.4%; median 3.5%) There are no workplace studies on all or randomly selected workers.

In the only available cross-sectional study on an occupational risk (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.

After the analysis of human data RAC concours with the Dossier Submitter that the frequency of positive reactions to 2,2'-ethylenedioxydiethyl dimethacrylate in diagnostic patch tests (median 3.5%) is above ≥ 2.0 %, a guidance value for high frequency. However, there is no adequate information enabling the assessment of true exposure of humans to the substance. According to the Guidance on the Application of the CLP Criteria: "*the concept of 'guidance' should be applied generally to all of the numeric criteria – they represent indicators derived from expert opinion and are not to be taken as proven absolute values. Application of this guidance should permit sub-categorisation where the human data on exposure and sensitisation is clear*". In this case a data on dermal exposure leading to skin sensitisation do not exist, therefore it is not possible to subcategorise a potency based on human data. On the other hand, according to Regulation (EC) 1272/2008, point 3.4.2.2.4.2.: "*Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis."* In case of 2,2'-ethylenedioxydiethyl dimethacrylate, both animal and human data provide sufficient evidence on skin sensitisation, and there is no conflict between results of animal and human data. However, only animal data provide clear information on the level of exposure needed to induce skin sensitisation. Similar judgement on the exposure is not possible for the human data. Therefore, in the opinion of RAC, 2,2'-ethylenedioxydiethyl dimethacrylate warrants classification as **Skin Sens. 1B; H317,** based on results of key LLNA study, while other positive GPMT and studies on humans support the classification of 2,2'-ethylenedioxydiethyl dimethacrylate as a skin sensitiser, although they are not conclusive for subcategorization.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).