Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

Tetramethylene dimethacrylate

EC Number: 218-218-1
CAS Number: 2082-81-7

CLH-O-0000007058-72-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

26 November 2021

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Tetramethylene dimethylacrylate

EC Number: 218-218-1

CAS Number: 2082-81-7

Index Number: Not available

Contact details for dossier submitter: **Finnish Competent Authority**
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ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON TETRAMETHYLENE DIMETHYLACRYLATE

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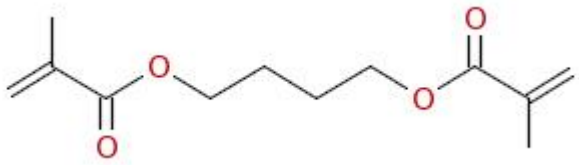
1 IDENTITY OF THE SUBSTANCE

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)	4-(2-methylprop-2-enoyloxy)butyl 2-methylprop-2-enoate 4-[(2-methylprop-2-enoyl)oxy]butyl 2-methylprop-2-enoate Butadiene dimethacrylate Butane-1,4-diyl bis(2-methylacrylate) Tetramethylene dimethacrylate
Other names (usual name, trade name, abbreviation)	1,4-butanediol dimethacrylate BDMA; 1,4-BDDMA
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	218-218-1
EC name (if available and appropriate)	Tetramethylene dimethacrylate
CAS number (if available)	2082-81-7
Other identity code (if available)	-
Molecular formula	C12H18O4
Structural formula	
SMILES notation (if available)	CC(=C)C(=O)OCCCCOC(=O)C(C)=C
Molecular weight or molecular weight range	226.27 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)	95-99.63 % (w/w)

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)
Tetramethylene dimethacrylate (CAS 2082-81-7)	95-99.63 % (w/w)	No entry in Annex VI	Eye Irrit. 2; H319 Skin Irrit. 2; H315 STOT SE 3; H335 Skin Sens. 1B; H317 Skin Sens. 1; H317

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	-	Tetramethylene dimethacrylate	218-218-1	2082-81-7	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	-	Tetramethylene dimethacrylate	218-218-1	2082-81-7	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	**Harmonised 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 tetramethylene 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 tetramethylene dimethacrylate and there have been no previous classification and labelling discussions of the substance.

As of June 2020, the C&L Inventory contains in total 159 notifications for tetramethylene dimethacrylate with respect to skin sensitisation:

- Skin Sens. 1 (64 notifications)
- Skin Sens. 1B (95 notifications)

Furthermore, 110 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. Tetramethylene 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 tetramethylene 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 (including by hand) or blending, and the products may be used with rollers or brushes or via dipping or pouring. Tetramethylene dimethacrylate is one of the most commonly patch tested (meth)acrylates that quite often induces positive reactions in clinical patients. There are over 100 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

Tetramethylene dimethacrylate is used in different coating products, fillers, putties, plasters, modelling clay, paints, adhesives and sealants. 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 tetramethylene dimethacrylate was used as the main data source for this CLH report. The unpublished full study reports were made available to the DS by the lead registrant.

In addition, open literature publications and patient exposure 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	-23°C at 1025 hPa	Anonymous 2006a	Measured OECD TG 102/EU Method A.1; differential scanning calorimetry
Boiling point	Not determined	Anonymous 2006a	No boiling point was detected prior to polymerisation at ca. 211°C at 1025 hPa OECD TG 103/EU Method A.2; differential scanning calorimetry
Relative density	1.024 at 20°C	Anonymous 2007	Measured OECD TG 109/DIN 51757; oscillating densitimeter method
Vapour pressure	0.1 Pa at 20°C	Anonymous 2006b	Measured OECD TG 104/EU Method A.4; dynamic method
Surface tension	Not assessed	REACH registration dossier	Based on chemical structure, no surface activity is to be expected. The test substance is not used as detergent.
Water solubility	243 mg/L at 20°C	Anonymous 2001	Measured OECD TG 105; flask method
Partition coefficient n-octanol/water	Log P_{ow} 3.10 at 20°C	Anonymous 2010	Measured OECD TG 117/EU Method A.8; HPLC method
Flash point	139°C at 1013.25 hPa	Anonymous 2008a	Measured EU Method A.9; Pensky-Martens closed-cup method
Flammability	Not flammable	REACH registration dossier	Study technically not feasible (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	290°C at 101 325 Pa	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

Property	Value	Reference	Comment (e.g. measured or estimated)
			structure.
Granulometry	Not applicable	REACH registration dossier	The substance is a liquid and is marketed or used in a non solid or granular form.
Stability in organic solvents and identity of relevant degradation products	Not assessed	REACH registration dossier	Stability of the substance is not considered critical; the substance has no particular reactivity towards typical solvents and is not used in solution.
Dissociation constant	Not assessed	REACH registration dossier	The substance does not contain any ionic, dissociable structures.
Viscosity	5.29 mm²/s at 20°C and 3.13 mm²/s at 40°C	Anonymous 2008b	Measured OECD TG 114/DIN 51562; Micro-Ubbelohde viscometer

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: 1,4-butanediol dimethacrylate Purity: not specified	Duration: phase I 120 min (samples collected at 0, 2, 5, 15, 30, 60 and 120 min), phase II 5 min (samples collected at 0 and 5 min) Concentrations: 0.25 mM (phase I), 0.05, 0.1 and 5.0 mM (phase II) Negative controls in the rat liver microsome experiments included incubations with heat-inactivated microsomes, no microsomes and no NADPH. Positive control: methyl methacrylate	Test substance was rapidly converted to methacrylic acid (MAA) in whole rat blood (phase I) and rat liver microsomes (phase II) with hydrolysis half-lives of 4.10 min (blood) and 4.46 min (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. V_{max} (in vitro) = 129 nmol/min/mg V_{max} (in vivo) = 160 mg/h/g liver K_m (in vitro) = 83 µm K_m (in vivo) = 19 mg/L	Anonymous (2013a)
Dermal absorption study (in silico modelling) Non-guideline Non-GLP Key study Reliability: 2 Test material: 1,4-butanediol dimethacrylate	The physicochemical parameters of M_W, log P and saturated aqueous solubility were used in the evaluation of 56 methacrylate compounds using a human skin model. 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 1,4-butanediol dimethacrylate is 2.895 µg/cm²/h, indicating low relative dermal absorption.	Anonymous (2013b)

Method	Remarks	Results	Reference
Purity: not specified			
Basic toxicokinetics in vitro and in vivo (read-across) Non-guideline GLP: not specified Key study Reliability: 1 Test material: methyl methacrylate (MMA) Lot: 98/15 Purity: > 99%	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	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.	Anonymous (2002)
Basic toxicokinetics in vitro (read-across) Non-guideline GLP Supporting study Reliability: 2 Test material: methyl methacrylate (MMA) Purity: not specified	Duration: phase I 120 min (samples collected at 0, 2, 5, 15, 30, 60 and 120 min), phase II 5 min (samples collected at 0 and 5 min) Negative controls in the rat liver microsome experiments included incubations with heat-inactivated microsomes, no microsomes and no NADPH.	The test substance was rapidly converted to methacrylic acid (MAA) in whole rat blood (phase I) and rat liver microsomes (phase II) with hydrolysis half-lives of 63 min (blood) and 0.29 min (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. V_{max} (in vitro) = 475 nmol/min/mg V_{max} (in vivo) = 128 mg/h/g liver K_m (in vitro) = 289 µm K_m (in vivo) = 29 mg/L	Anonymous (2013c)

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

A few toxicokinetic studies are available for tetramethylene dimethacrylate and structurally similar methyl methacrylate (MMA) (Table 8Table 8). Tetramethylene dimethacrylate has a molecular weight of 226.27 g/mol and it is in liquid form at 20°C. Water solubility of the substance is 243 mg/L at 20°C, and the octanol-water partition coefficient (log P_{OW}) is 3.10.

Absorption

In general, the physico-chemical properties (molecular weight, physical state, water solubility, lipophilicity) of tetramethylene dimethacrylate favour absorption from the gastrointestinal tract.

The vapour pressure of the substance is 0.1 Pa at 20°C. 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 tetramethylene dimethacrylate from the respiratory tract.

On the basis of the molecular weight, tetramethylene 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). Furthermore, the log P_{OW} (3.10) favours penetration into the stratum corneum and hence absorption across the skin. The predicted steady-state flux is 2.895 μg/cm²/h (Anonymous 2013b). The ester bonds of tetramethylene 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. Tetramethylene dimethacrylate is unlikely to be absorbed via inhalation.

Distribution

Since tetramethylene 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 high permeability across lipid membranes (log P_{OW} 3.10), 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 tetramethylene dimethacrylate.

Metabolism

Ester hydrolysis is the primary step in the metabolism of methacrylate esters. In the case of diol di-methacrylate esters (such as tetramethylene 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, 1,4-butanediol. Tetramethylene 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 4.46 minutes in rat liver microsomes and 4.10 minutes in whole rat blood. Similar metabolic pattern has been identified for a structurally similar substance, methyl methacrylate; it 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.

The primary methacrylic metabolite of tetramethylene dimethacrylate, methacrylic acid, will predominantly be metabolized in the liver through the valine pathway and the citric acid cycle (Cosmetic Ingredient Review

2005). 1,4-butanediol is, in turn, known to be rapidly transformed to gamma-hydroxybutyric acid and subsequently to succinic semialdehyde (NTP 1996). The aldehyde is then converted to succinic acid, which is degraded via the citric acid cycle.

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, such as tetramethylene dimethacrylate.

Excretion

The parent compound tetramethylene dimethacrylate is not likely to be excreted as such due to the rapid hydrolysis of the ester bonds. The metabolites of the substance will be cleared from blood circulation by physiological pathways, and the majority of the received dose will eventually be exhaled as CO_2.

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 (including purity), vehicle, positive control	Dose levels, duration of exposure	Results	Reference
LLNA OECD TG	CBA/CaOlaHsd female mice	Tetramethylene dimethacrylate, purity	25, 50 and 100%	**Sensitising** The SI values at 25, 50 and	Anonymous (2014)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance (including purity), vehicle, positive control**	**Dose levels, duration of exposure**	**Results**	**Reference**
429 (2010) GLP Key study Reliability: 1 A pre-test was performed in 2 mice with concentrations of 50 and 100% to determine the highest non-irritant test concentration.	5 per each treatment group, 5 in control group (vehicle only)	99.63% Vehicle: acetone:olive oil (4+1 v/v), purity of the acetone 99.6% Positive control: α-hexylcinnamaldehyde (CAS 101-86-0) in acetone:olive oil (4:1)	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 (20.0 µCi ^{3}HTdR per mouse, volume: 250 µl) on day 6. Necropsy on day 6	100% were 2.74, 3.76, and 5.72, respectively. EC3 value: 31.4% (w/v) Observations: no mortality occurred during the study. On day 3, all treated animals showed reduced spontaneous activity, ruffled fur and hunched posture. The animals treated with concentrations of 50 and 100% showed eyelid closure and abnormal walk on day 3, and ruffled fur on day 4. 2/5 of the animals treated with a concentration 100% showed reduced spontaneous activity on day 4. All treated animals developed an erythema of the ear skin during the observation period (25%: score 1 on days 3 and 4; 50%: score 1 on days 3-5; 100%: score 1 on days 2 and 6, score 2 on days 3-5). Body weight was within normal range.	
GPMT OECD TG 406 (1981) GLP: not specified Reliability: 3 Supporting study A pre-test was performed to determine the highest non-irritant test concentration.	SSc:Al outbred female guinea pigs No. of animals not specified (with other chemicals in the same paper, 10-20 animals per test group had been used)	1,4-butanediol dimethacrylate (purity not specified, but obtained from commercial sources, hence, commercial grade assumed) Vehicle: soybean oil or sbomek (soybean oil:2-butanone, 1:2) (intradermal induction), petrolatum (topical induction and challenge) 10% sodium lauryl sulphate (SLS) was used on day 7 as an adjuvant prior to topical induction. Positive control: not specified	Induction (day 0): 1% intradermal injection Induction (day 8): 5% topical application Challenge (day 21): 25% topical application	**Not sensitising** No further information available	Anonymous (1984a)
Freund´s complete	Dunkin-Hartley female guinea	1,4-butanediol dimethacrylate, purity	0.5 M (13%) for intradermal	**Sensitising**	Anonymous

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance (including purity), vehicle, positive control**	**Dose levels, duration of exposure**	**Results**	**Reference**
adjuvant test Non-guideline GLP: not specified Reliability: 3 Weight of evidence A pre-test was performed to determine the highest non-irritant test concentration.	pigs 8 animals in the treatment group, 4-6 animals in the control group	97% Vehicle (topical induction and challenge): Aramek (methyl ethyl ketone:arachis oil 2:1) Positive control: not specified	induction exposure (days 1-9) and 3 M (78%) for challenge and rechallenge exposures (days 21 and 35)	After challenge on day 21 8/8 animals were sensitised, after rechallenge on day 35 5/8 animals were positive.	(1983a)
GPMT Non-guideline GLP: not specified Reliability: 2 Weight of evidence A pre-test was performed to determine the highest non-irritant test concentration.	Himalayan white spotted female guinea pigs 10 animals in the treatment group, 6 animals in the control group	1,4-butanediol dimethacrylate, purity 97% Vehicle (topical induction): petrolatum or 80% ethanol Vehicle (challenge): Aramek (methyl ethyl ketone:arachis oil 2:1) Positive control: not specified	0.5 M (13%) for intradermal induction exposure (day 0), 100% for topical induction exposure (day 7), 1 M (26%) for challenge and rechallenge exposures (days 21 and 35)	**Ambiguous** After challenge on day 21 0/10 animals were sensitised, after rechallenge on day 35 2/10 animals were positive. According to the authors, a third challenge has been perfomed on day 49 which confirmed the results of the rechallenge, but the data are not shown in the publication.	Anonymous (1983b)
GPMT Non-guideline GLP: not specified Reliability: 2 Weight of evidence A pre-test was performed on three animals to determine the highest non-irritant test concentration.	Dunkin-Hartley female guinea pigs 10 animals in the treatment group, 10 animals in the control group	1,4-butanediol dimethacrylate, purity min. 95% Vehicle (intradermal induction): olive oil:acetone 9:1 Vehicle (topical induction, challenge and rechallenge): petrolatum Before topical induction, a pretreatment with 10% SLS (w/w) in petrolatum was used. Positive control: not specified	2% (w/w) for intradermal induction exposure, 50% for topical induction and 1% (w/w) for challenge and rechallenge exposures (amount of test item ca. 0.015 g) 48 hours after the first challenge the animals received a booster dose intradermally (2%, without Freund's	**Not sensitising** 0/10 animals were sensitised in this test; however, it is not documented whether the scores were obtained after the first or second challenge.	Anonymous (1984b)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance (including purity), vehicle, positive control	Dose levels, duration of exposure	Results	Reference
			complete adjuvant).		

Animal data

The sensitising potential of tetramethylene dimethylacrylate has been investigated in one murine local lymph node assay and in four guinea pig studies (Table 9).

LLNA

The LLNA was conducted in accordance with OECD test guideline 429 (2010) and principles of GLP (Anonymous 2014). A pre-test was performed in two animals with concentrations of 50 and 100% to determine the highest non-irritant test concentration. The mouse treated with the undiluted test substance showed slightly reduced spontaneous activity, and an erythema of the ear skin was observed in both animals (score 1 in the mouse treated with 50% concentration, score 1-2 in the mouse treated with 100% concentration). Furthermore, scabby ears were observed on day 5 in the animal treated with the undiluted test substance.

In the main study, three treated groups of five CBA/CaOlaHsd female mice aged 8-9 weeks and weighing 17.8-22.3 g (mean 20.3 g ± 1.2 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 was observed during the study period. All treated animals showed unspecific clinical signs on day 3, including reduced spontaneous activity, ruffled fur and hunched posture. All tried to burrow themselves in the bedding one hour after the third application. Eyelid closure and abnormal walk were also observed in the mice treated with concentrations of 50 and 100%. On day 4, all animals treated with concentrations of 50 and 100% showed ruffled fur and two animals treated with the undiluted test substance showed reduced spontaneous activity. According to the authors, it cannot be confirmed whether these symptoms were signs of systemic toxicity or mere reactions to the irritant nature of the test substance. 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 2.74, 3.76, and 5.72 were determined at concentrations of 25, 50 and 100%, respectively (Table 10). The EC3 value was 31.4% (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	2740.8	353.5	2.74
50	3757.0	1373.9	3.76
100	5714.8	1986.8	5.72

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

In a GPMT study (mainly in accordance with the OECD test guideline 406, 1981), female guinea pigs (no. of animals not specified) were induced on day 0 with 1% intradermal injections of tetramethylene dimethacrylate in the nape of the neck (Anonymous 1984a). The animals weighed 300-350 g at the initiation of the study and were approximately one month old. Purity of the test substance is not specified in the study report. On day 7, approximately 250 mg of 10% sodium lauryl sulphate (instead of Freund´s adjuvant, as described in the test guideline) in petrolatum was gently massaged into the neck and left uncovered for 24 hours. Epicutaneous application of 5% tetramethylene dimethacrylate followed on day 8, and the dressing containing the test solution was left in place for 48 hours. The vehicle controls received the same treatment, but with an equivalent amount of petrolatum. Challenge exposure was performed on day 21 using an occlusive epicutaneous application with a 25% concentration, and readings were made on days 23 and 24 (after 48 and 72 hours, respectively). The vehicle controls received identical treatment. The test substance was not found to be sensitising in the study. There is no further information available on clinical signs or findings.

A Freund´s complete adjuvant test (FCAT) and a GPMT were conducted together on groups of eight and ten albino female guinea pigs, respectively (Anonymous 1983a, 1983b). The purity of tetramethylene dimethacrylate was 97% in both studies. According to the authors, sensitisation to impurities cannot be completely excluded. The animals weighed 350-450 g at study initiation, but their ages are not specified in the study report. There were four to six animals in the control group in the FCAT and six animals in the control group in the GPMT. A pre-test with FCA-treated animals preceded both studies. In both the FCAT and the GPMT, the animals were induced with intradermal injections of 0.5 M tetramethylene dimethacrylate which, according to the authors, corresponds to a 13% concentration. In the FCAT, 3 M (78%) concentration was then used for challenge and rechallenge exposures. In the GPMT, a 100% concentration was used for the topical induction exposure and 1 M (26%) concentration was used for challenge and rechallenge exposures. For the closed patch induction on day 7 of the GPMT, petrolatum or 80% ethanol was used as a vehicle. Aramek (methyl ethyl ketone:arachis oil 2:1) was used as a vehicle in all challenges. Tetramethylene dimethacrylate was found to be sensitising in the FCAT, but the results in the GPMT were ambiguous. There is no information on mortality or clinical signs or findings in either of the studies.

In a GPMT study (in accordance with the method described by Magnusson and Kligman), 10 female albino guinea pigs weighing 300-400 g (ages not specified) were treated with tetramethylene dimethacrylate intradermal injection (2%) in olive oil/acetone to induce sensitisation (Anonymous 1984b). There were 10 guinea pigs in the control group. The animals were further sensitised by topical application of 50% tetramethylene dimethacrylate. Prior to topical induction, the animals were treated with 10% sodium lauryl sulphate in petrolatum. For challenge and rechallenge exposures, a concentration of 1% tetramethylene dimethacrylate in petrolatum was used. A booster dose was applied intradermally on the neck using the same concentration and vehicle 48 hours after the first challenge. The rechallenge occurred one week after the first challenge. None of the animals were sensitised in this test, but it is not documented whether the scores were obtained after the first or the second challenge. No clinical observations or macroscopical findings are described in the study report.

Human data

A total of 26 clinical studies have been identified for tetramethylene dimethacrylate (Table 11). The studies comprised a total of 128 patients who tested positive to the substance. In all studies, the diagnostic method was patch testing. Data on skin exposure to tetramethylene 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	Reference
CASE REPORTS ON SINGLE CASES				
Case report	Tetramethylene dimethacrylate (2%, Chemotechnique's test substance i.e. in pet.)	A 38-year-old female was sensitised to a glue used in the attachment of car rear-view mirrors to the windscreen (with 6 years of work history). 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, and she developed rhinitis, paresthesia of fingertips and gastrointestinal complaints.	13 acrylic compounds provoked mild to extreme allergic reactions in a patch test. Positive reaction to test substance (++ on day 2, ++ on day 3, ++ on day 4). Tetramethylene dimethacrylate was not mentioned in the safety data sheet of the glue or detected in chemical analysis.	Kanerva et al. (1995)
Case report	Tetramethylene 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 reactions to the test substance (+ was the strongest reading on days 2, 3 and 4) Tetramethylene dimethacrylate was not detected in chemical analyses of the nail products.	Kanerva et al. (1996)
Case report	Tetramethylene dimethacrylate (concentration and vehicle not defined)	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. Tetramethylene dimethacrylate reaction was + at 96 hours.	Paley et al. (2006)
PATIENT SERIES				
Patient series	Tetramethylene dimethacrylate (2% in pet.)	7 patients occupationally sensitized to methacrylate-based dental composite products	1 patient reacted positively to the test substance out of 5 patients tested (20%). The test substance was not mentioned in safety data sheets of the products.	Kanerva et al. (1989)
Patient series	Tetramethylene	126 dental technicians were	Positive reaction to the test	Peiler et al.

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
	dimethacrylate (2% in pet.), purity 97%	tested with (meth)acrylates in 1995-1999 in Department of Dermatology, Städtische Kliniken (Dortmund, DE)	substance in 6 of 126 patients (4.8%), all the reactions were assessed clinically relevant i.e. the sensitised persons had handled tetramethylene dimethacrylate-containing products. Authors considered that the test substance was a weak sensitiser in comparison to methyl methacrylate due to low number of positive reactions despite common exposure.	(2000)
Patient series	Tetramethylene dimethacrylate (2% 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.	Positive reaction to the test substance in 5 of 72 patients (6.9%) who were positive to some (meth)acrylate.	Geukens & Goossens (2001)
Patient series	Tetramethylene 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.	In dentists sensitised to acrylic resins, 8 of 20 patients (40%) reacted positively to the test substance. There were no positive reactions to the test substance in dental nurses.	Kiec-Swierczynska & Krecisz (2002)
Patient series	Tetramethylene dimethacrylate (2% in pet.)	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	24 patients reacted to some (meth)acrylate. 16 of these patients were tested with the test substance, and 3 of them tested positive (18.8%). It is unclear how many patients in total were tested with tetramethylene dimethacrylate.	Goon et al. (2007)
Patient series	Tetramethylene dimethacrylate (2% in pet.)	473 patients were tested with a (meth)acrylate series at 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.	Positive reactions to the test substance in 3 cases: 1 dentist (++ reaction), 1 dental nurse (++ reaction) and 1 dental technician (+ reaction). Tetramethylene dimethacrylate was not mentioned in safety data sheets of the products used by these 3 patients.	Aalto-Korte et al. (2007)
Patient series	Tetramethylene	473 patients were tested with a	Positive reaction to the test	Aalto-Korte et

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
	dimethacrylate (2% in pet.)	(meth)acrylate series at Finnish Institute of Occupational Health (Helsinki, FI) in 1994-2006. Among 61 patients with allergic reaction to some (meth)acrylate, 10 patients with present occupational exposure to acrylic glues were identified.	substance in 4 (40%) of 10 patients (++ in three patients, +++ in one patient). All 4 patients had handled methacrylate-based glues but tetramethylene dimethacrylate was not mentioned in the safety data sheets of the glues.	al. (2008)
Patient series	Tetramethylene dimethacrylate (0.1% 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 4 Spanish hospitals in 2013-2016	Positive reaction to the test substance in 1 patient out of 7 (20%) tested with the substance within the group of 43 patients.	Gatica-Ortega (2017)
Patient series	Tetramethylene 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 2 of 16 patients (12.5%).	Fisch et al. (2019)
Patient series	Tetramethylene 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, positive reaction to the test substance in 6 of 26 patients (23.1%) tested with the substance.	Marrero-Alemán et al. (2019)
CROSS-SECTIONAL STUDIES ON RISK OCCUPATIONS				
Cross-sectional study	Tetramethylene dimethacrylate (2% in pet.)	A questionnaire was sent to 1132 dental technicians and 173 answered. 55 cases were patch tested.	Tetramethylene dimethacrylate was positive in 1 (2%) case of those tested (N=55).	Rustemeyer & Frosch (1996)
Cross-sectional study	Tetramethylene dimethacrylate (Chemotechnique's test substance i.e. 2% in pet.)	49 out of 1038 dental technicians voluntarily participated in a study on patch testing at the Department of Dermatology in the Catholic University of Korea (Seoul, KR)	Positive reaction to the test substance in 1 case, 2.1% of those tested. 7 patients were positive to some acrylic substance. The test substance-positive case constituted 14% of this group.	Lee et al. (2001)
CLINICAL PATCH TEST DATA ON SELECTED PATIENTS (AIMED TESTING WITH ACRYLIC COMPOUNDS)				
Patch test data, selected patients	Tetramethylene 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 2 (9.5%) dentists out of 21 patients tested with the substance.	Kiec-Swierczynska (1996)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Patch test data, selected patients	Tetramethylene dimethacrylate (2% in pet.)	The incidence of allergic reactions to certain methacrylates by the Information Network of Departments of Dermatology (Göttingen, DE) in 1992-1995	Positive reaction to the test substance in 13 of 2971 patients (0.4%).	Schnuch (1996)
Patch test data, selected patients	Tetramethylene 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 1885-1995	Positive reaction to the test substance in 10 of 274 (3.6%) patients tested with the substance. 48 patients reacted positively to some (meth)acrylate. The test substance-positive cases constituted 20.8% of these.	Kanerva et al. (1997)
Patch test data, selected patients	Tetramethylene 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 identified and patch tested with (meth)acrylates	Positive reaction to the test substance in 7 of 255 patients (2.7%) tested with the substance.	Tucker & Beck (1999)
Patch test data, selected patients	Tetramethylene dimethacrylate (concentration or vehicle not stated)	A retrospective study on patients patch tested with dental screening series in 7 dermatology clinics in Finland in 1994-1998	There were 13 (0.5%) allergic reactions to the test substance in the 2408 patients tested. The frequency of allergic reactions varied between 0.1% and 2.2% in different clinics.	Kanerva et al. (2001)
Patch test data, selected patients	Tetramethylene 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 6 (5.5%) of 109 patients tested with (meth)acrylates. 24 patients had allergic reactions to some (meth)acrylate. The 6 test substance-positive cases constituted 25% of these.	Wrangsjö et al. (2001)
Patch test data, selected patients	Tetramethylene 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 9 (0.5%) out of 1642 patients tested. 48 patients reacted positively to at least one (meth)acrylate. The test substance-positive cases constituted 18.8% of these patients.	Goon et al. (2006)
Patch test data, selected patients	Tetramethylene dimethacrylate (2% in pet.)	A retrospective study on 451 patients suspected of having occupational contact dermatitis and tested with a (meth)acrylate series at Finnish Institute of	Positive reaction to the test substance in 9 patients (2.0%) 66 patients reacted positively to at least one (meth)acrylate.	Aalto-Korte et al. (2010) Includes the patients in

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		Occupational Health (Helsinki, FI) in 1994-2009	The test substance-positive cases constituted 13.6% of this group.	Aalto-Korte et al. (2008) and Aalto-Korte et al. (2007)
Patch test data, selected patients	Tetramethylene 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 of 151 (4.0%) patients tested with the substance. 24 patients reacted positively to some (meth)acrylate. The positive reactions to tetramethylene dimethacrylate constituted 25% of these.	Christoffers et al. (2013)
Patch test data, selected patients	Tetramethylene 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 5 (4.1%) patients. 37 patients reacted positively to (meth)acrylates. The tetramethylene dimethacrylate-positive cases constituted 13.5% of these.	Ramos et al. (2014)
Patch test data, selected patients	Tetramethylene 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 10 (2.1%) patients tested with the substance. 52 patients reacted positively to (meth)acrylates. The positive reactions to tetramethylene dimethacrylate constituted 19% of these.	Spencer et al. (2016)

Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and 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 in 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 tetramethylene dimethacrylate in general population or unselected clinical patients.

Tetramethylene dimethacrylate has been commonly tested as part of the (meth)acrylate series since the 1980s. Its established test concentration is 2% in petrolatum. A total of 11 diagnostic patch test studies on selected patients could be identified for the substance. The frequency of positive reactions varied between 0.4% and 9.5% (median 2.7%).

No strict workplace studies could be identified for tetramethylene dimethacrylate. However, two cross-sectional studies on dental technicians, who are at risk of developing a contact allergy due to exposure to acrylic compounds at work, share a similar design. Only the workers with skin symptoms were patch tested in these studies. The frequency of positive patch test reactions to the substance was 2% in both studies (1/55 and 1/49 of the tested patients; Rustemeyer & Frosch 1996, and Lee et al. 2001, respectively).

The rest of the identified studies were either case reports of single cases (n=4) or reports describing patient series (n=10) without clearly stating the frequency of reaction to tetramethylene dimethacrylate in all patients tested during the same time period. Specific exposure to the substance was described by Peiler et al. (2000) in all six dental technicians who tested positive to it. In the 1990s in Germany, tetramethylene dimethacrylate was commonly found in the products used by dental technicians and virtually all workers were exposed to the substance. The authors considered that tetramethylene dimethacrylate was a weak sensitiser compared to methyl methacrylate because the frequency of contact allergy was low (4.8%), despite common exposure. Dental technicians' skin exposure to tetramethylene dimethacrylate may also vary within countries, as for instance in Finland only two dental technicians out of eight had used products containing the substance (Aalto-Korte et al. 2007).

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

No other data is available.

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

Animal data

In the key LLNA (OECD TG 429, 2010), three treated groups of five mice were administered tetramethylene 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 was observed during the study period. All treated animals showed unspecific clinical signs on day 3, including reduced spontaneous activity, ruffled fur and hunched posture. All tried to burrow themselves in the bedding one hour after the third application. Eyelid closure and abnormal walk were also observed in the mice treated with concentrations of 50 and 100%. On day 4, all animals treated with concentrations of 50 and 100% showed ruffled fur and two animals treated with the undiluted test substance showed reduced spontaneous activity. According to the authors, it cannot be confirmed whether these symptoms were signs of systemic toxicity or mere reactions to the irritant nature of the test substance. A dose-related increase in the stimulation index (SI) values was observed and the threshold positive value of 3 was exceeded at concentrations of 50% and 100%. The EC3 value was 31.4% (w/v).

Four guinea pig studies conducted in the 1980s are also available for evaluation of skin sensitisation potential of tetramethylene dimethacrylate. Only one of them, Anonymous 1984a, complies with the OECD test guideline (TG 406, 1981), although with clear deviations (number of animals and positive control not specified, purity of the substance not known) and therefore not suitable for classification purposes. The remaining three studies, a non-guideline Freund´s complete adjuvant test (FCAT) and two non-guideline GPMTs, are of better methodological quality, apart from their unspecified positive controls and a rather low number of animals (Anonymous 1983a, 1983b and 1984b). Tetramethylene dimethacrylate was found to be sensitising in the FCAT (8/8 sensitised animals after the first challenge, 5/8 sensitised animals after rechallenge) (Anonymous 1983a). The substance was not a skin sensitiser in one GPMT, whereas the results were ambiguous in the other (Anonymous 1984b and Anonymous 1983b, respectively).

Human data

A total of 26 clinical patch test studies were identified for tetramethylene dimethacrylate. There are no studies in general population or unselected clinical patients. Tetramethylene dimethacrylate is usually tested as part of the (meth)acrylate patch test series, and a total of 11 diagnostic patch test studies on selected patients could be identified for the substance. The frequency of positive reactions varied between 0.4% and 9.5% (median 2.7%) in the studies.

There are no strict workplace studies for tetramethylene dimethacrylate. However, in two cross-sectional studies dental technician was identified as a risk occupation for contact allergy following exposure to acrylic compounds, such as tetramethylene dimethacrylate. The rest of the identified studies were either case reports

of single cases (n=4) or reports describing patient series (n=10) without clearly stating the frequency of reaction to the substance in all patients tested during the same time period.

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), tetramethylene dimethacrylate showed an EC3 value of 31.4% (w/v), indicating a low to moderate skin sensitisation potency. Sub-category 1A can therefore be excluded. According to the Guidance on the Application of the CLP Criteria (ECHA 2017b, Table 3.4.4), the results allow classification in Skin Sens. 1B. Four guinea pig tests from the 1980s are also available for assessment; however, due to their methodological limitations, they mainly serve as supporting information to be used as part of a weight-of-evidence evaluation.

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**	**Tetramethylene 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 %	11 studies 0.4%-9.5% (median 2.8%)
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 %	2 studies: 2%
Number of published cases	≥ 100 cases	< 100 cases	128 patch-test-positive cases

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

Frequencies of positive patch tests in 11 selected dermatitis patient materials (aimed testing) have varied between 0.4% and 9.5% (median 2.7%), but they are mostly above the limit of high frequency.

There are no workplace studies on all or randomly selected workers. In two cross-sectional studies on dental technicians mimicking workplace studies (on selected workers) the frequency of positive patch tests was 2%, i.e. above the cut-off value of 1.0% for high frequency.

The number of published patch-test-positive cases, 128, also exceeds the cut-off value for high frequency (≥ 100).

Positive patch test reactions to tetramethylene dimethacrylate are relatively common in patients sensitised to methacrylates, but specific exposure to the substance in sensitised or tested patients has rarely been described in the literature. Both the exposure and the lack of exposure to tetramethylene dimethacrylate are typically difficult to assess in clinical work due to the unavailability of chemical analyses. Positive test reactions may also arise from cross-reactivity to other methacrylates, yet true exposure to tetramethylene dimethacrylate in clinical patients cannot be excluded. Of the identified literature, only Peiler et al. (2000) confirmed exposure to the substance in all six dental technicians who gave a positive reaction to it.

To conclude, the frequency of positive reactions to tetramethylene dimethacrylate in diagnostic patch tests can be considered high. However, there is no adequate information enabling the assessment of true exposure to the substance. Animal data is sufficient for sub-categorization, and human data supports the classification of tetramethylene dimethacrylate as a skin sensitiser. Based on the key LLNA, Sub-category 1A can be excluded and Sub-category 1B is justified.

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 **Sub-category 1B**. The corresponding hazard statement is **H317: May cause an allergic skin reaction**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) assessed the skin sensitising property of tetramethylene dimethylacrylate using the available human data and the results of five animal studies: one murine local lymph node assay (LLNA) and four guinea pig studies.

Animal studies

1.The **LLNA** was conducted in accordance with OECD TG 429 (2010) and principles of GLP (Anonymous 2014) and is considered as reliable (Reliability score 1) and as key study by DS. A pre-test was performed in two animals with concentrations of 50 and 100% to determine the highest non-irritant test concentration. The mouse treated with the undiluted test substance showed slightly reduced spontaneous activity, and an erythema of the ear skin was observed in both animals (score 1 in the mouse treated with 50% concentration, score 1-2 in the mouse treated with 100% concentration). Furthermore, scabby ears were observed on day 5 in the animal treated with the undiluted test substance. In the main study, three treated groups of five CBA/CaOlaHsd female mice aged 8-9 weeks and weighing 17.8-22.3 g (mean 20.3 g ± 1.2 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 was observed during the study period. All treated animals showed unspecific clinical signs on day 3, including reduced spontaneous activity, ruffled fur and hunched posture. In this study, Stimulation Indices of 2.74, 3.76, and 5.72 were determined at concentrations of 25, 50 and 100%, respectively and EC3 value was 31.4% (w/v).

2. The first **guinea-pig study** (Anonymous 1984a) was conducted according to OECD TG 406 but GLP conditions were not specified. The DS has assigned to this study reliability score of 3. The female guinea pigs (no. of animals not specified) were induced on day 0 with 1% intradermal injections of tetramethylene dimethylacrylate. Purity of the test substance is not specified in the study report. On day 7, approximately 250 mg of 10% sodium lauryl sulphate in petrolatum was gently

massaged into the neck and left uncovered for 24 hours. Epicutaneous application of 5% tetramethylene dimethacrylate followed on day 8, and the dressing containing the test solution was left in place for 48 hours. The vehicle controls received the same treatment, but with an equivalent amount of petrolatum. Challenge exposure was performed on day 21 using an occlusive epicutaneous application with a 25% concentration, and readings were made on days 23 and 24 (after 48 and 72 hours, respectively). The vehicle controls received identical treatment. Positive control not specified. The test substance was not found to be skin sensitising in the study.

3. The second guinea-pig study, a non-guideline Freund´s complete adjuvant test (FCAT), GLP conditions not specified, was conducted on groups of eight albino female guinea pigs (Reliability score 3) (Anonymous 1983a). The purity of tetramethylene dimethacrylate was 97%. According to the authors, sensitisation to impurities cannot be completely excluded. There were four to six animals in the control group in the FCAT. A pre-test with FCA-treated animals preceded both studies. The animals were induced with intradermal injections of 0.5 M tetramethylene dimethacrylate which, according to the authors, corresponds to a 13% concentration. The 3 M (78%) concentration was used for challenge and rechallenge exposures. Aramek mixture of methyl ethyl ketone:arachis oil 2:1 was used as a vehicle for the closed patch induction and for challenge tests. There is no information on mortality or clinical signs. After challenge 8/8 animals were sensitised on day 21, after rechallenge 5/8 animals were positive on day 35.

4. In the third guinea pig study (Reliability score 2) the sensitisation potential of tetramethylene dimethacrylate was examined in a non-guideline guinea pig maximisation test with no specified GLP (Anonymous 1983b). The study was done with Himalayan white spotted female guinea pigs with 10 animals in the treatment group and 6 animals in the control group. The animals were induced with intradermal injections of 0.5 M tetramethylene dimethacrylate which, according to the authors, corresponds to a 13% concentration. Undiluted substance was for topical induction exposure (day 7). The 1 M (26%) concentration was used for challenge and rechallenge exposures on days 21 and 36. Petrolatum or 80% ethanol was used as a vehicle for the topical induction. For challenge tests Aramek mixture of methyl ethyl ketone:arachis oil 2:1 was used as a vehicle. There is no information on mortality or clinical signs. After challenge on day 21 0/10 animals were sensitised, after rechallenge on day 35 2/10 animals were positive. According to the authors, a third challenge has been performed on day 49 which confirmed the results of the rechallenge, but the data are not shown in the publication.

5. In the fourth guinea pig study (Reliability score 2) 10 female Dunkin-Hartley guinea pigs each received tetramethylene dimethacrylate at concentration of 2% (w/w) in olive oil/acetone for intradermal induction, 50% in petrolatum for topical induction, and 1% (w/w) in petrolatum for challenge and rechallenge exposures (test item amount equivalent of ca. 0.015 g) (Anonymous, 1984b). Ten animals were used in the

control group. Before topical induction, a pre-treatment with 10% sodium lauryl sulphate (w/w) in petrolatum was used. Positive control is not specified. A booster dose was applied intradermally on the neck using the same concentration and vehicle 48 hours after the first challenge. The rechallenge occurred one week after the first challenge. None of the animals were sensitised in this test, but it is not documented whether the scores were obtained after the first or the second challenge. No clinical observations or macroscopical findings are described in the study report.

Human data

A total of 26 clinical studies have been identified for tetramethylene dimethacrylate (Table 11). The studies comprised a total of 128 patients who tested positive to the substance. In all studies, the diagnostic method was patch testing. Data on level and frequency of skin exposure to tetramethylene dimethacrylate is scarce.

Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and was 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 in 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 tetramethylene dimethacrylate in general population or unselected clinical patients.

Type of data/report	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
CASE REPORTS ON SINGLE CASES				
Case report	Tetramethylene dimethacrylate (2%, Chemotechnique's test substance i.e. in petrolatum)	A 38-year-old female was sensitised to a glue used in the attachment of car rear-view mirrors to the windscreen (with 6 years of work history). She developed a dry and fissured dermatitis on fingers and palms of both hands. The dermatitis spread within a couple of	13 acrylic compounds provoked mild to extreme allergic reactions in a patch test. Positive reaction to test substance (++ on day 2, ++ on day 3, ++ on day 4). Tetramethylene dimethacrylate was not mentioned in the safety data sheet of the glue	Kanerva *et al*. (1995)

		weeks to lower arms, chest, neck and face, and she developed rhinitis, paresthesia of fingertips and gastrointestinal complaints.	or detected in chemical analysis.	
Case report	Tetramethylene 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 reactions to the test substance (+ was the strongest reading on days 2, 3 and 4) Tetramethylene dimethacrylate was not detected in chemical analyses of the nail products.	Kanerva *et al*. (1996)
Case report	Tetramethylene dimethacrylate (concentration and vehicle not defined)	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. Tetramethylene dimethacrylate reaction was + at 96 hours.	Paley *et al*. (2006)
PATIENT SERIES				
Patient series	Tetramethylene dimethacrylate (2% in petrolatum)	7 patients occupationally sensitized to methacrylate-based dental composite products	1 patient reacted positively to the test substance out of 5 patients tested (20%). The test substance was not mentioned in safety data sheets of the products.	Kanerva *et al*. (1989)
Patient series	Tetramethylene dimethacrylate (2% in petrolatum), purity 97%	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 6 of 126 patients (4.8%), all the reactions were assessed clinically relevant i.e. the sensitised persons had handled	Peiler *et al*. (2000)

			tetramethylene dimethacrylate-containing products. Authors considered that the test substance was a weak sensitiser in comparison to methyl methacrylate due to low number of positive reactions despite common exposure.	
Patient series	Tetramethylene dimethacrylate (2% in petrolatum)	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.	Positive reaction to the test substance in 5 of 72 patients (6.9%) who were positive to some (meth)acrylate.	Geukens & Goossens (2001)
Patient series	Tetramethylene dimethacrylate (2% in petrolatum)	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.	In dentists sensitised to acrylic resins, 8 of 20 patients (40%) reacted positively to the test substance. There were no positive reactions to the test substance in dental nurses.	Kiec-Swierczynska & Krecisz (2002)
Patient series	Tetramethylene dimethacrylate (2% in petrolatum)	90 patients suspected of having dermatitis caused by (meth)acrylates were patch tested at the Department of Occupational and Environmental Dermatology (Malmö, SE) in	24 patients reacted to some (meth)acrylate. 16 of these patients were tested with the test substance, and 3 of them tested positive (18.8%). It is unclear how	Goon *et al*. (2007)

		1995-2004	many patients in total were tested with tetramethylene dimethacrylate.	
Patient series	Tetramethylene dimethacrylate (2% in petrolatum)	473 patients were tested with a (meth)acrylate series at 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.	Positive reactions to the test substance in 3 cases: 1 dentist (++ reaction), 1 dental nurse (++ reaction) and 1 dental technician (+ reaction). Tetramethylene dimethacrylate was not mentioned in safety data sheets of the products used by these 3 patients.	Aalto-Korte *et al*. (2007)
Patient series	Tetramethylene dimethacrylate (2% in petrolatum)	473 patients were tested with a (meth)acrylate series at Finnish Institute of Occupational Health (Helsinki, FI) in 1994-2006. Among 61 patients with allergic reaction to some (meth)acrylate, 10 patients with present occupational exposure to acrylic glues were identified.	Positive reaction to the test substance in 4 (40%) of 10 patients (++ in three patients, +++ in one patient). All 4 patients had handled methacrylate-based glues but tetramethylene dimethacrylate was not mentioned in the safety data sheets of the glues.	Aalto-Korte *et al*. (2008)
Patient series	Tetramethylene dimethacrylate (0.1% in petrolatum)	A retrospective study on 43 patients diagnosed with allergic contact dermatitis caused by (meth)acrylates in long-lasting nail polish at dermatology departments of 4 Spanish hospitals in 2013-2016	Positive reaction to the test substance in 1 patient out of 7 (20%) tested with the substance within the group of 43 patients.	Gatica-Ortega (2017)
Patient series	Tetramethylene	A retrospective	Positive reaction to	Fisch *et al*.

	dimethacrylate (2% in petrolatum)	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	the test substance in 2 of 16 patients (12.5%).	(2019)
Patient series	Tetramethylene dimethacrylate (2% in petrolatum)	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, positive reaction to the test substance in 6 of 26 patients (23.1%) tested with the substance.	Marrero-Alemán *et al*. (2019)
CROSS-SECTIONAL STUDIES ON RISK OCCUPATIONS				
Cross-sectional study	Tetramethylene dimethacrylate (2% in petrolatum)	A questionnaire was sent to 1132 dental technicians and 173 answered. 55 cases were patch tested.	Tetramethylene dimethacrylate was positive in 1 (2%) case of those tested (N=55).	Rustemeyer & Frosch (1996)
Cross-sectional study	Tetramethylene dimethacrylate (Chemotechnique's test substance i.e. 2% in petrolatum)	49 out of 1038 dental technicians voluntarily participated in a study on patch testing at the Department of Dermatology in the Catholic University of Korea (Seoul, KR)	Positive reaction to the test substance in 1 case, 2.1% of those tested. 7 patients were positive to some acrylic substance. The test substance-positive case constituted 14% of this group.	Lee *et al*. (2001)
CLINICAL PATCH TEST DATA ON SELECTED PATIENTS (AIMED TESTING WITH ACRYLIC COMPOUNDS)				
Patch test data, selected patients	Tetramethylene dimethacrylate (2% in petrolatum)	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 2 (9.5%) dentists out of 21 patients tested with the substance.	Kiec-Swierczynska (1996)

Patch test data, selected patients	Tetramethylene dimethacrylate (2% in petrolatum)	The incidence of allergic reactions to certain methacrylates by the Information Network of Departments of Dermatology (Göttingen, DE) in 1992-1995	Positive reaction to the test substance in 13 of 2971 patients (0.4%).	Schnuch (1996)
Patch test data, selected patients	Tetramethylene dimethacrylate (2%; Chemotechnique's test substance i.e. in petrolatum)	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 1885-1995	Positive reaction to the test substance in 10 of 274 (3.6%) patients tested with the substance. 48 patients reacted positively to some (meth)acrylate. The test substance-positive cases constituted 20.8% of these.	Kanerva *et al*. (1997)
Patch test data, selected patients	Tetramethylene dimethacrylate (2%, Chemotechnique's test substance i.e. in petrolatum)	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 identified and patch tested with (meth)acrylates	Positive reaction to the test substance in 7 of 255 patients (2.7%) tested with the substance.	Tucker & Beck (1999)
Patch test data, selected patients	Tetramethylene dimethacrylate (concentration or vehicle not stated)	A retrospective study on patients patch tested with dental screening series in 7 dermatology clinics in Finland in 1994-1998	There were 13 (0.5%) allergic reactions to the test substance in the 2408 patients tested. The frequency of allergic reactions varied between 0.1% and 2.2% in different clinics.	Kanerva *et al*. (2001)
Patch test data, selected patients	Tetramethylene dimethacrylate (2% in petrolatum)	109 patients (all dental personnel) were tested with a dental screening	Positive reaction to the test substance in 6 (5.5%) of 109 patients tested	Wrangsjö *et al*. (2001)

		series at the Department of Occupational and Environmental Dermatology (Stockholm, SE) in 1995-1998	with (meth)acrylates. 24 patients had allergic reactions to some (meth)acrylate. The 6 test substance-positive cases constituted 25% of these.	
Patch test data, selected patients	Tetramethylene dimethacrylate (2% in petrolatum)	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 9 (0.5%) out of 1642 patients tested. 48 patients reacted positively to at least one (meth)acrylate. The test substance-positive cases constituted 18.8% of these patients.	Goon *et al*. (2006)
Patch test data, selected patients	Tetramethylene dimethacrylate (2% in petrolatum)	A retrospective study on 451 patients suspected of having occupational contact dermatitis and tested with a (meth)acrylate series at Finnish Institute of Occupational Health (Helsinki, FI) in 1994-2009	Positive reaction to the test substance in 9 patients (2.0%) 66 patients reacted positively to at least one (meth)acrylate. The test substance-positive cases constituted 13.6% of this group.	Aalto-Korte *et al*. (2010) Includes the patients in Aalto-Korte *et al*. (2008) and Aalto-Korte *et al*. (2007)
Patch test data, selected patients	Tetramethylene dimethacrylate (2%; Chemotechnique's test substance i.e. in petrolatum)	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 of 151 (4.0%) patients tested with the substance. 24 patients reacted positively to some (meth)acrylate. The positive reactions to tetramethylene dimethacrylate constituted 25% of these.	Christoffers *et al*. (2013)

Patch test data, selected patients	Tetramethylene dimethacrylate (2% in petrolatum)	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 5 (4.1%) patients. 37 patients reacted positively to (meth)acrylates. The tetramethylene dimethacrylate-positive cases constituted 13.5% of these.	Ramos *et al*. (2014)
Patch test data, selected patients	Tetramethylene dimethacrylate (2% in petrolatum)	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 10 (2.1%) patients tested with the substance. 52 patients reacted positively to (meth)acrylates. The positive reactions to tetramethylene dimethacrylate constituted 19% of these.	Spencer *et al*. (2016)

Tetramethylene dimethacrylate has been commonly tested as part of the (meth)acrylate series since the 1980s. Its established test concentration is 2% in petrolatum. A total of 11 diagnostic patch test studies on selected patients could be identified for the substance. The frequency of positive reactions varied between 0.4% and 9.5% (median 2.7%).

No strict workplace studies could be identified for tetramethylene dimethacrylate. However, two cross-sectional studies on dental technicians who are at risk of developing a contact allergy due to exposure to acrylic compounds at work, share a similar design. Only the workers with skin symptoms were patch tested in these studies. Frequency of positive patch test reactions to the substance was 2% in both studies (1/55 and 1/49 of the tested patients; Rustemeyer & Frosch 1996 and Lee *et al*. 2001, respectively).

The rest of the identified studies were either case reports of single cases (n=4) or reports describing patient series (n=10) without clearly stating the frequency of reaction to tetramethylene dimethacrylate in all patients tested during the same time period.

Specific exposure to the substance was described by Peiler *et al*. (2000) in all six

dental technicians who tested positive to it. In the 1990s in Germany, tetramethylene dimethacrylate was commonly found in the products used by dental technicians and virtually all workers were exposed to the substance. The authors considered that tetramethylene dimethacrylate was a weak sensitiser compared to methyl methacrylate because the frequency of contact allergy was low (4.8%), despite common exposure. Dental technicians' skin exposure to tetramethylene dimethacrylate may also vary within countries, as for instance in Finland only two dental technicians out of eight had used products containing the substance (Aalto-Korte *et al*. 2007).

Based on the available data, the DS has proposed classification as **Skin Sens. 1B** with hazard statement **H317: May cause an allergic skin reaction**.

Comments received during consultation

One MSCA supported proposed classification as **Skin Sens. 1B** with hazard statement **H317: May cause an allergic skin reaction** based on results of the key animal study, and human data as supportive evidence.

One Company-Importer agreed with the harmonised classification as **Skin Sens. 1B, H317**, mainly based on animal data, namely LLNA data. This Company noted that human data support the classification and labelling in a weight of evidence approach and do not allow a sub-categorisation due to the absence of exposure information.

One MSCA noted that in the view of the DS the outcome of an LLNA indicates that tetramethylene dimethylacrylate should be classified as skin sensitiser in sub-category 1B and ask the DS to assess in more detail the clinical findings that have been observed during the study, such as:

- "Trying to burrow oneself in the bedding" observed one hour after the third application,
- "Ruffled fur", "Hunched posture" and "Reduced spontaneous activity % observed on 3rd day after application of the substance on surface of ears at concentrations of 25 and 50% and on day 3 and 4 after application of substance at concentration of 100%"
- "Eyelid closure" and "Abnormal walk" observed on 3rd day after application of the substance on surface of ears at concentrations of 50 and 100%

In the opinion of the MSCA, it is crucial to discuss the above-mentioned clinical findings in more detail because they may have an influence on the acceptability of the LLNA to be used as basis for sub-categorisation. Assessment of these findings is advisable because OECD testing guideline 429 specifies with respect to dose selection "that the highest concentration maximises exposure while avoiding systemic toxicity" (see OECD TG 429, par. 18).

In response to this comment the DS noted that the assessment relies on the full study report of the LLNA and that it does not have access to more detailed

information. An acute dermal toxicity study conducted with the substance is not available. There is only a supporting study available on a closely related read-across substance 1,3-BDDMA. The study is poorly reported. No clinical signs or other effects were observed. The acute dermal LD50 of 1,3-BDDMA is reported to be >3000 mg/kg bw in rabbit. Acute oral toxicity LD50 of 1,3-BDDMA (rat, combined) is reported to be 10 066 mg/kg bw. The study has been performed according to the OECD TG 401. As the substance is not acutely toxic by the oral route this supports findings that 1,3-BDDMA is not acutely toxic by the dermal route either.

In the first LLNA study (Anonymous 2014), the unspecific clinical symptoms reduced spontaneous activity, ruffled fur and hunched posture may in general indicate mild systemic toxicity. These effects were observed in all treated animals on day 3 (25%: 1h after the third application; 50% and 100%: 1h before and 1h after the third application). Furthermore, the animals in mid and high dose groups showed eyelid closure and abnormal walk. No marked reduction in body weight nor mortality was observed during the study period. According to the authors, it cannot be confirmed whether these symptoms were signs of systemic toxicity or mere reactions to the irritant nature of the test substance. However, the study was considered valid by the authors. In the registration dossier the study is reliable without restrictions with Klimisch score 1. Skin irritation in test animals was not excessive as the erythema scores varied between 1 and 2 (<3). It cannot be concluded if the effects observed were reactions to the irritant nature of the substance. Without any more detailed information on the clinical signs and, taking into account that there was no relevant body weight loss, it is difficult to conclude on systemic toxicity either. Nevertheless, the DS noted that slight clinical signs were observed in the study and that they might indicate systemic toxicity.

One MSCA noted that based on the weight of evidence, including both human and animal data, it should be concluded that a classification as skin sensitiser is warranted for tetramethylene dimethacrylate. In relation to sub-categorization, MSCA is of the opinion that, when available, adequate human data should always be preferred over animal data to conclude on classification.
The MSCA is of the view that sufficient information is available to conclude on exposure of the substance, at least for some categories of workers. MSCA considers that both frequency of occurrence of skin sensitisation and frequency of exposure of worker should be concluded to be high. Similarly, the workers in the field of long-lasting nail polishing might be considered highly exposed to tetramethylene dimethacrylate. Based on human data, MSCA is of the opinion that tetramethylene dimethacrylate should be classified as Skin Sens. 1 without sub-categorization, because in line with the CLP guidelines, relatively high frequency of occurrence of skin sensitisation and relatively high frequency of exposure (score 5-6) support such decision. The MSCA also noted that in the key LLNA the animals showed clinical signs indicating acute systemic toxicity from 50% and 100% concentrations (eyelid closure and abnormal walk on day 3, and ruffled fur on day 4; reduced spontaneous activity

on day 4 at the highest dose) while according to the OECD 429 guidance on LLNA, the highest concentration should be selected in order to "maximise exposure while avoiding systemic toxicity and/or excessive local skin irritation". Therefore the dose selection of this LLNA using concentrations of 25%, 50% and 100% is questionable.

In response on evaluation of human data, the DS pointed out that the assessment of human exposure was not included in the CLH report because there are no adequate data available to allow a reliable evaluation of the exposure to the specific substance. There is a lack of data on the products containing the substance. Therefore, it is not possible to know the concentration or dose humans are exposed to. The same applies for information of repeated exposure and the number of exposures. In view of the DS, only assumptions can be made on human exposure as there is no reported information of the exact exposure. Therefore, basing an evaluation on assumptions and to use it to conclude on the classification requires great care.

Regarding the LLNA the DS has agreed that the test concentrations were high. In the pre-test with 2 animals on day 4, the mice treated with the undiluted test substance showed transiently a slightly reduced spontaneous activity. An erythema of the ear skin was observed in both animals (at 50%: score 1 on days 3-6; at 100%: score 1 on days 2, 3 and 6, and score 2 on days 4-5). Furthermore, scabby ears were observed on day 5 in the animal treated with 100% test substance. Increase in ear thickness on day 6 was 6% and 3% in mouse treated with 50 and 100 % test substance, respectively. No relevant change in body weights was observed. According to the study authors "The highest concentration tested was the highest level that could be achieved whilst avoiding systemic toxicity and excessive local skin irritation as confirmed in the pre-test". The concentrations of 25, 50 and 100% were selected for the main test. According to the OECD TG 429: "Excessive local skin irritation is indicated by an erythema score ≥3 and/or an increase in ear thickness of ≥25% on any day of measurement". No excessive local skin irritation was observed in pre-test animals as erythema scores were 1-2 (<3) and increase in ear thickness was not more than 6% (<25%). The DS notes the substance has self-classification as Skin Irrit. 2, however, according to data in the registration dossier the substance is not a skin irritant. OECD TG 429 states also that "The highest dose selected for the main LLNA study will be the next lower dose in the pre-screen concentration series that does not induce systemic toxicity and/or excessive local skin irritation". It is unclear why the concentration of 100% was selected for the main test. In the main test all treated animals showed a slight or moderate erythema of the ear skin (at 25%: score 1 on days 3-4; at 50%: score 2 on days 3-5; at 100%: score 1 on days 2 and 6) but there was no excessive skin irritation.

The unspecific clinical symptoms reduced spontaneous activity, ruffled fur and hunched posture were observed in all treated animals on day 3 (at 25%: 1h after the third application; at 50% and 100%: 1h before and 1h after the third application). Furthermore, the animals in mid and high dose groups showed eyelid closure and

abnormal walk. A loss in body weight or mortality was not observed in any of animals treated with test substance during the study period. According to the authors, it cannot be confirmed whether these symptoms were signs of systemic toxicity or mere reactions to the irritant nature of the test substance. The study was considered valid by the authors. In the registration dossier the study is reliable without restrictions with Klimisch score 1. It cannot be concluded if the effects observed in LLNA were reactions to the irritant nature of the substance. Without any more detailed information on the clinical signs, and taking into account that there was no relevant body weight loss, it is difficult to conclude on systemic toxicity either. The DS notes that slight clinical signs were observed in the study and they might indicate systemic toxicity.

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.*"

Animal data

In case of tetramethylene dimethacrylate both human data and animal data were provided, but in line with the above statement the animal data are analysed first. Results of five animal studies are available: one LLNA and four guinea pig studies. The LLNA (Anonymous 2014) was assessed with reliability index 1 and used by the DS as a key study.

In the public discussion reliability of this LLNA has been questioned due to high doses or concentrations used in the test. It has been pointed out that in the pre-test and the main study tetramethylene dimethacrylate was inducing toxic symptoms in treated mice (at 25, 50 and 100% reduced spontaneous activity, ruffled fur and hunched posture, and at 50 and 100% additionally eyelid closure and abnormal walk on day 3). It is noted that none of the symptoms indicating narcotic effects of tetramethylene dimethacrylate were reported in treated mice 5 and 6 days after exposure, and that this is indicating the effects were reversible. No effect on survival and body weight gain were observed and therefore the symptoms may be considered as an evidence of

slight systemic toxicity. Such a conclusion is supported by OECD TG 429 recommendations on excessive systemic toxicity findings: "*the following clinical observations may indicate systemic toxicity when used as part of an integrated assessment and therefore may indicate the maximum dose level to use in the main LLNA: changes in nervous system function (e.g. pilo-erection, ataxia, tremors, and convulsions); changes in behaviour (e.g. aggressiveness, change in grooming activity, marked change in activity level); changes in respiratory patterns (i.e. changes in frequency and intensity of breathing such as dyspnea, gasping, and rales), and changes in food and water consumption. In addition, signs of lethargy and/or unresponsiveness and any clinical signs of more than slight or momentary pain and distress, or a >5% reduction in body weight from Day 1 to Day 6, and mortality should be considered in the evaluation of systemic toxicity. Moribund animals or animals obviously in pain or showing signs of severe and enduring distress should be humanely killed* ". The authors of the study did not report such symptoms. The symptoms observed in mice in this LLNA are considered as an evidence of slight toxicity which is not expected to affect assessment of skin sensitisation in this test.

On the other hand, the study authors were unable to decide whether these symptoms were signs of systemic toxicity or mere reactions to the irritant nature of the test substance. The DS has provided additional information indicating that intensity of irritation was relatively low (score 1 and 2), and an increase in ear thickness on day 6 was 6% and 3% in animals treated with 50 and 100 % test substance, respectively. According to the OECD TG 429, "Excessive local skin irritation is indicated by an erythema score ≥3 and/or an increase in ear thickness of ≥25% on any day of measurement". No excessive local skin irritation was observed in animals as erythema scores were 1-2 (<3) and increase in ear thickness was not more than 6% (<25%). Taking into account the above analysis RAC considers that the LLNA is valid and its results can be used for evaluation of classification of tetramethylene dimethacrylate.

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 the data are sufficient.Care should be taken when classifying 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 based on a Local lymph node assay, a value of EC3 should be ≤ 2 % while that for the subcategory 1B should be > 2 %. 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 a SI ≥ 3 meeting the CLP criteria for sub-category 1A. The results of LLNA (Anonymous, 2014) indicate that tetramethylene dimethacrylate did not induce a Stimulation Index above 3 at concentration of 25%, and therefore it will not induce such a Stimulation Index a concentration 10 times lower, therefore classification of this substance to category 1A can be excluded and sub-categorization is possible. Tetramethylene dimethacrylate has induced Stimulation Index above 3 at concentration 50% and

100%, with EC3 meeting classification criteria for category 1B (calculated to be 31.4%). Since classification in subcategory 1A can be excluded, tetramethylene dimethacrylate warrants classification to category 1B based on results of LLNA.

Only one out of four skin sensitisation studies on guinea pigs (Anonymous 1983a) with reliability score 3 was positive. In the study all 8 animals given in intradermal induction tetramethylene dimethacrylate at concentration of 13% had positive response in the challenge test at concentration of 78% providing supportive evidence for skin sensitisation properties of tetramethylene dimethacrylate. Since only one concentration was used, this study does not provide data for sub-categorization.

Three other guinea pig studies (Anonymous 1983b with reliability score 2; Anonymous 1984a with reliability score 3; Anonymous 1984b with reliability score 2) did not disclose skin sensitising potential of tetramethylene dimethacrylate, what might be interpreted that skin sensitising potency of this substance 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 can include the following type of data (ECHA 2017b, Section 3.4.2.2.3.1.), respectively:

	Human data
Sub-category 1A	(d) positive responses at ≤ 500 µg/cm2 (HRIPT, HMT – induction threshold); (e) 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; (f) 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):

Human diagnostic patch test data	**High frequency**	**Low/moderate frequency**	**Tetramethylene 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 %	11 studies 0.4%-9.5% (median 2.8%)
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 2 studies: 2%
Number of published cases	≥ 100 cases	< 100 cases	128 patch-test-positive cases

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

Frequencies of positive patch tests in 11 selected dermatitis patient materials (aimed testing) vary between 0.4% and 9.5% (median 2.7%) but are mostly above the limit of high frequency (≥ 2.0 %).

There are no workplace studies on all or randomly selected workers. In two cross-sectional studies on dental technicians, mimicking workplace studies (on selected workers), the frequency of positive patch tests was 2%, i.e., above the cut-off value of 1.0% for high frequency.

The number of published patch-test-positive cases, 128, also exceeds the cut-off value for high frequency (≥ 100).

Positive patch test reactions to tetramethylene dimethacrylate are relatively common in patients sensitised to methacrylates, but specific exposure to the substance in sensitised or tested patients has rarely been described in the literature. Both the exposure and the lack of exposure to tetramethylene dimethacrylate are typically difficult to assess in clinical work due to the unavailability of chemical analyses. Positive test reactions may also arise from cross-reactivity to other methacrylates, yet true exposure to tetramethylene dimethacrylate in clinical patients cannot be excluded. Of the identified literature, only Peiler *et al*. (2000) confirmed exposure to

the substance in all six dental technicians who gave a positive reaction to it.

After analysis of human data, RAC concours with the DS that the frequency of positive reactions to tetramethylene dimethacrylate in diagnostic patch tests (median 2.8%) are above 2.0 %, the guidance threshold 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 data on dermal exposure leading to skin sensitisation do not exist. Therefore, it is not possible to sub-categorise 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 tetramethylene 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 a clear information on level of exposure needed to induce skin sensitisation while a judgement on the exposure level is not possible based on human data. In the opinion of RAC tetramethylene dimethacrylate warrants a classification as **Skin Sens. 1B; H317** based on results of the key LLNA study. The other positive Guinea pig studies and studies on humans support the classification of tetramethylene dimethacrylate as a skin sensitiser, although they are not conclusive for sub-categorization.

After analysis of human data, RAC concours with the DS that the frequency of positive reactions to tetramethylene dimethacrylate in diagnostic patch tests can be considered high. However, there is no adequate information enabling the assessment of true exposure to the substance. Animal data is sufficient for sub-categorization, and human data supports the classification of tetramethylene dimethacrylate as a skin sensitiser. Based on the key LLNA, sub-category 1A can be excluded and **sub-category 1B is justified**.

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 Bioaccumulation

Not assessed in this dossier.

11.4 Acute aquatic hazard

Not assessed in this dossier.

11.5 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 tetramethylene 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

Confidential Annex on toxicokinetic studies