CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate

EC Number: 276-957-5

CAS Number: 72869-86-4

Index Number: Not available

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Finnish Safety and Chemicals Agency (Tukes)
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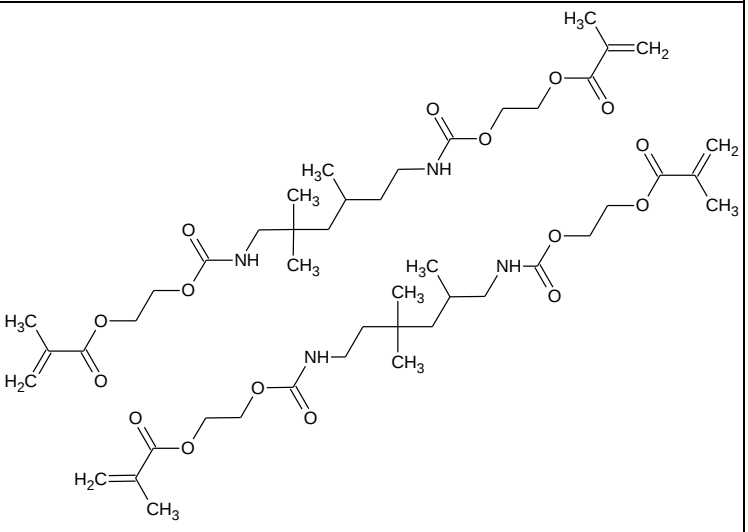
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

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

Name(s) in the IUPAC nomenclature or other international chemical name(s)	2-[({2,2,4-trimethyl-6-[({2-[(2-methylprop-2-enoyl)oxy]ethoxy}carbonyl)amino]hexyl}carbamoyl)oxy]ethyl 2-methylprop-2-enoate 2-[({2,4,4-trimethyl-6-[({2-[(2-methylprop-2-enoyl)oxy]ethoxy}carbonyl)amino]hexyl}carbamoyl)oxy]ethyl 2-methylprop-2-enoate
Other names (usual name, trade name, abbreviation)	7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate Urethane methacrylate (aliphatic) UDMA
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	276-957-5
EC name (if available and appropriate)	7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate
CAS number (if available)	72869-86-4
Other identity code (if available)	-
Molecular formula	$C_{23}H_{38}N_2O_8$
Structural formula	
SMILES notation (if available)	CC(CCNC(=O)OCCOC(=O)C(C)=C)CC(C)(C)CNC(=O)OCCOC(=O)C(C)=C.CC(CNC(=O)OCCOC(=O)C(C)=C)CC(C)(C)CCNC(=O)OCCOC(=O)C(C)=C

Molecular weight or molecular weight range	470.56 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	A multi-constituent substance containing structural isomers and stereoisomers
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)	-

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)**
7,7,9 (or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate (CAS 72869-86-4)	Confidential	No entry in Annex VI	Skin Sens. 1; H317 Skin Sens. 1B; H317 Aquatic Chronic 2; H411 Aquatic Chronic 3; H412 Eye Irrit. 2; H319 Skin Irrit. 2; H315 STOT SE 3; H335
7,7,9-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate (CAS 41137-60-4)	Confidential	-	-
7,9,9-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate (CAS 74389-53-0)	Confidential	-	-

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

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Confidential	0-0.5 %	Skin Sens. 1; H317	-	No

The impurity has been taken into account in the classification of the substance. The dossier submitter (DS) considers that the impurity does not have an impact on the hazard assessed and on the proposed classification for the substance. Details on the impurity are considered confidential. Further information is provided in confidential Annex.

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	-	7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate	276-957-5	72869-86-4	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	-	7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate	276-957-5	72869-86-4	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 7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate (UDMA) there is no harmonised classification available, as the substance is not listed in Annex VI to the

Regulation (EC) No 1272/2008 (CLP Regulation). According to the SCCS (Scientific Committee on Consumer Safety) opinion, the substance is a weak sensitiser (SCCS 2018).

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 UDMA and there have been no previous classification and labelling discussions of the substance.

As of June 2020, the C&L Inventory contains in total 212 notifications for UDMA with respect to skin sensitisation:

- Skin Sens. 1 (165 notifications)
- Skin Sens. 1B (47 notifications)

Furthermore, two 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 DS disagrees with the self-classifications Skin Sens. 1 and no classification proposed by the notifiers. UDMA is registered under REACH, and it is manufactured and/or imported in the European Economic Area in 100-1000 tonnes per year. The widespread use of the substance supports action at community level: exposure to UDMA is anticipated under circumstances of professional, industrial and consumer use, mainly via dermal route. Workers may be in direct contact with formulated products containing the substance during mixing or blending, and the products may be used with rollers or brushes or via spraying, dipping or pouring. UDMA has been patch tested in clinical patients since the 1980s with the (meth)acrylate series, and it regularly induces positive reactions in some patients. There are over 100 published cases with a positive patch test reaction to UDMA, which exceeds the limit for high frequency of occurrence of skin sensitisation.

5 IDENTIFIED USES

UDMA is used in adhesives and sealants, coating products, polymers, inks and toners, laboratory chemicals and cosmetics and personal care products. It is also used in printing and recorded media reproduction, health services and scientific research and development, as well as for the manufacture of wood and wood products, pulp, paper and paper products and plastic products. The substance is used by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

6 DATA SOURCES

The REACH registration dossier of UDMA 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 Clear to slightly opalescent, slightly yellowish	REACH registration dossier	Observed
Melting/freezing point	Not determined	Anonymous (2006)	No melting point; the substance solidifies amorphously in the glassy state at ca. -36°C. OECD TG 102/EU Method A.1; differential scanning calorimetry
Boiling point	Not determined	Anonymous (2016)	No endothermic effect (boiling) could be detected up to the decomposition temperature of 140 °C. OECD TG 103/EU Method A.2; differential scanning calorimetry
Relative density	1.112 at 20°C	Anonymous (2007a)	Measured DIN 51757; oscillating densitimeter
Vapour pressure	2.32 x 10E-06 hPa at 20°C 2.62 x 10E-06 hPa at 25°C	Anonymous (2009a)	Estimated OECD TG 104/EU Method A.4; calculated using a linear regression equation
Surface tension	52.09 mN/m at 20°C and 10.161 mg/L	Anonymous (2009b)	Measured OECD TG 115/EU Method A.5; tensiometer The substance is surface active.
Water solubility	11.29 ± 0.256 mg/L at 20°C	Anonymous (2009c)	Measured OECD TG 105/EU Method A.6; column elution method
Partition coefficient n-octanol/water	log P_{ow} = 3.39 at 20°C (pH not measured)	Anonymous (2007b)	Measured OECD TG 117/EU Method A.8; HPLC method
Flash point	> 100°C at 1013 hPa	Anonymous (2009d)	Measured EU Method A.9; Pensky-Martens closed-cup method Polymerization of the substance occurs at high temperatures; no flash point up to 100°C.
Flammability	Not flammable	REACH registration dossier	Based on flash point and boiling point the substance is a non-flammable liquid. The substance has no flash point up to 100°C.

Property	Value	Reference	Comment (e.g. measured or estimated)
			Based on the chemical structure, pyrophoricity and flammability on contact with water are not expected. The substance is a liquid. A liquid shows not self-heating behaviour if it is not absorbed on a large surface.
Explosive properties	Not explosive	REACH registration dossier	There are no chemical groups associated with explosive properties in the molecule.
Self-ignition temperature	445 °C at 998 hPa	Anonymous (2009e)	Measured EU Method A.15; Auto-ignition temperature
Oxidising properties	Not oxidising	REACH registration dossier	On the basis of the chemical structure the substance is incapable of reacting exothermically with combustible materials.
Granulometry	Not applicable	REACH registration dossier	The substance is a liquid and not marketed or used in a non solid or granular form.
Stability in organic solvents and identity of relevant degradation products	No information available	-	-
Dissociation constant	No information available	-	-
Viscosity	8000-13 000 mPA*s at 25°C	Rahn GmbH (2020) (personal communication)	Measured DIN 53019

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

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

No toxicokinetic studies are available for UDMA. However, in accordance with the Guidance on Information Requirements and Chemical Safety Assessment, toxicokinetic behaviour of a substance may also be predicted from its toxicological and physico-chemical properties (ECHA 2017a). The molecular weight of UDMA is 470.56 g/mol. The substance is a liquid at 20°C, and its water solubility is 11.29 mg/L at the same temperature. The octanol-water partition coefficient (log P_{OW}) is 3.39.

Absorption

Absorption is a function of the potential for a substance to diffuse across biological membranes (ECHA 2017a). It is dependent upon many factors, such as the molecular structure and weight, particle size, water solubility and octanol-water partition coefficient (log P_{OW}).

Oral:

The molecular weight of UDMA falls below the general cut-off value of 500 g/mol for small molecules, therefore favouring oral absorption. The substance is moderately soluble in aqueous media (solubility > 1 mg/L) and its log P_{OW} is in the range of -1 and 4, which indicate that it is capable of dissolving in the gastrointestinal fluids and permeating the lipid membrane of the gastrointestinal tract.

Oral toxicity data can also be used in the evaluation of oral absorption, because the presence of signs of systemic toxicity indicates that absorption has occurred (ECHA 2017a). In an acute oral toxicity study (conducted according to OECD test guideline 401 and under GLP conditions), five male and five female rats were administered a bolus dose of UDMA (5000 mg/kg bw) by gavage (Ullmann 1984a). There was no mortality. On day 1, all males and all females showed dyspnea until five hours after dosing. Other observations in all males and all females included ruffled fur (1-2 hours after dosing) and a curved body position (1-3 hours after dosing). There were no other clinical signs during the rest of the 14-day observation period. The body weight of the animals was not affected, and no treatment-related macroscopic findings were noted at necropsy. In another acute oral toxicity study (similar to OECD test guideline 401), ten male and ten female rats were given 20 mL/kg bw (equivalent to 22.24 g/kg bw, based on a density value of 1.112 g/mL) UDMA by gavage (Sterner 1977a). One male died on day 7; redness of the mucous membrane in the stomach and intestine was observed at necropsy. A hard residue of the test substance was also observed in the stomach. None of the surviving animals showed any treatment-related effects at necropsy. Clinical observations included slightly reduced activity and general response 1-24 hours after dosing, in addition to increased abnormal gait (1-3 hours after dosing), piloerection (1-24 hours after dosing) and diarrhea (up to 7 days after dosing). All these symptoms were displayed in an unreported number of animals. The body weight of one female rat was reduced on day 14.

In a combined repeated dose toxicity/reproductive toxicity screening study (in accordance with OECD TG 422 and principles of GLP), UDMA was administered to male and female rats at doses of 100, 300 or 1000 mg/kg bw/day before and during mating as well as after mating (altogether 56 and 56, 57 or 64 days for males and females, respectively) (Anonymous 2017). The control group received vehicle only. Reversibility of effects observed was assessed following a 14-day recovery period in additional animals of the control and high dose groups. At 100 mg/kg bw/day, no treatment-related effects were observed. At 300 mg/kg bw/day, pale liver was observed in one male and hepatic lipidosis in three males. At 1000 mg/kg bw/day, pale liver and hepatic lipidosis were observed in both males and females with high incidence.

One important factor regarding the absorption of a substance via the gastrointestinal tract is the possibility of biotransformation. According to the Guidance on Information Requirements and Chemical Safety Assessment, structural alterations may occur as a result of metabolism by gastrointestinal flora, enzymes released into the gastrointestinal tract or by hydrolysis of the substance (ECHA 2017a). The ester bonds of UDMA are likely to be enzymatically hydrolysed in the gastrointestinal environment to corresponding acid and alcohol moieties, which will be absorbed more easily than the parent substance. Due to these alterations, the predictions based on the physico-chemical properties of the parent substance may no longer apply as such. In the absence of more specific hydrolysis data, absorption has to be assumed to cover a worst-case scenario; therefore, the potential for oral absorption is presumed to be high.

Inhalation:

The vapour pressure of UDMA is 2.32 x 10E-06 hPa at 20°C. This falls below the general cut-off value of 0.5 kPa, indicating very low volatility (ECHA 2017a). Therefore, under normal use and handling conditions, inhalation exposure and availability for respiratory absorption of the substance in the form of vapour, gases or mists is not considered significant. Solid particles, however, may be available for absorption after

inhalation of an aerosolized substance. Substances in a liquid form may readily diffuse or dissolve into the mucus lining the respiratory tract. Particles with an aerodynamic diameter greater than 100 µm have a low probability to be inhaled; in turn, particles with diameters below 50 µm may reach the thoracic region and those below 15 µm the alveolar region of the respiratory tract. Water solubility and log P_{OW} of UDMA both favour its absorption in the respiratory tract, but the high molecular weight of the substance (470.56 g/mol) is likely to be a limiting factor for pulmonary deposition. There is no information on acute or repeated dose inhalation toxicity. Based on its physicochemical properties, the potential of UDMA to be absorbed via inhalation is low.

Dermal:

Dermal absorption is dependent upon various factors, such as physical state, molecular weight and structure, water solubility, log P_{OW}, vapour pressure and surface tension (ECHA 2017a). For liquids and substances in solution, dermal uptake is higher than that of dry particulates. Molecular weights below 100 g/mol favour dermal uptake, while above 500 g/mol absorption of the molecule through an intact skin rapidly declines. UDMA is in liquid form at 20°C, but its molecular weight (470.56 g/mol) is on the border to be too large to be absorbed. Water solubility of UDMA (11.29 mg/L at 20°C) falls in the range of 1-100 mg/L, indicating low to moderate dermal absorption. Log P_{OW} of the substance (3.39) favours penetration into the stratum corneum and hence absorption across the skin. If the surface tension of an aqueous solution is below 10 mN/m, there is potential for increased dermal uptake. UDMA is a surface active agent, but its surface tension (52.09 mN/m at 20°C) exceeds this value.

Dermal toxicity data can also be used in the evaluation of dermal absorption, because the presence of signs of systemic toxicity indicates that absorption has occurred (ECHA 2017a). Skin irritation/corrosion studies and skin sensitisation studies may also provide useful information, because a damaged skin surface may enhance penetration in case of an irritant or corrosive substance, and skin sensitisation implies that some dermal uptake must have occurred (although it may only have been a small fraction of the total dose). In an acute dermal toxicity study, five male and five female rats were treated with 2000 mg/kg bw UDMA under semi-occlusive conditions (Holalagoudar 2016). No mortality, clinical signs or local effects were observed, and there were no treatment-related macroscopical findings at necropsy. Body weight and body weight gain remained within normal range. There is no animal data on long-term dermal exposure to UDMA.

Three albino rabbits (one male and two females) were treated with 0.5 mL of undiluted UDMA under occlusive conditions in a GLP-compliant acute dermal irritation/corrosion study similar to OECD test guideline 404 (Ullmann 1984b). The effects were recorded at 1, 24, 48 and 72 hours. No mortality occurred during the observation period. All the erythema and edema scores were 0 at all reading time points, and the body weights were unaffected. Another available in vivo skin irritation study is a Draize test, in which six albino rabbits were treated with 0.5 mL of undiluted UDMA under occlusive conditions (Sterner 1977b). The effects were recorded only at 0 and 48 hours. Directly after patch removal, five rabbits showed very slight to well-defined erythema (score 1-2) and two rabbits showed very slight edema (score 1). At 48 hours, the erythema and edema had cleared completely in all animals. No other observations are reported. In a local lymph node assay in mice, no signs of skin irritation were observed, but UDMA was found to be a skin sensitiser (Anonymous 2009f; see Section 10.7 for details). Proof of sensitisation after dermal contact hence indicates that a sufficient amount of UDMA is taken up via the dermal route to induce a positive reaction in the skin.

The ester bonds of UDMA 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. Considering all the available information, the estimated dermal absorption for UDMA is low.

Distribution

The concentration of a substance in blood or plasma is dependent on the dose, rates of absorption, distribution and elimination, and tissue affinity (typically described as volume of distribution) (ECHA 2017a). The most useful parameters providing information on distribution are molecular weight, water solubility and octanol-water partition coefficient (log P_{OW}). The smaller the molecule, the wider it is distributed within the body. As UDMA 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. Very lipophilic substances tend to concentrate in adipose tissue and may accumulate intracellularly. The parent compound UDMA has a high permeability across lipid membranes (log P_{OW} 3.39), but the degradation products do not contain any lipophilic groups. Thus, there is no indication of bioaccumulation potential.

The clinical signs and macroscopical observations in the acute and repeated dose oral toxicity studies indicate that UDMA is systemically available. However, no target organs can be identified based upon the necropsy findings and clinical chemistry parameters.

Metabolism

On the basis of physico-chemical information, in the absence of metabolism data, it is very difficult to predict the metabolic changes of a substance (ECHA 2017a). The ester bonds of UDMA are prone to phase I hydrolysis reactions by esterases. The degradation products may then be conjugated to increase the polarity of the molecule and hence facilitate its excretion or further metabolism.

Based on the information provided in the registration dossier of UDMA, the potential metabolites of the substance have been identified using the QSAR OECD toolbox. Twenty hepatic metabolites and two dermal metabolites were predicted for each of the main components, resulting from hydrolysis of the ester bonds and amino bond. One of the metabolites derived by the ester bond hydrolysis is the methacrylate group, which is rapidly converted to methacrylic acid. Methacrylic acid is then metabolized further mainly in the liver via the valine pathway and citric acid cycle (Cosmetic Ingredient Review 2005). Up to 98 metabolites were predicted to result from microbiological metabolism, but not all of these reactions are expected to occur in the human gastrointestinal tract.

Excretion

The predominant routes of excretion for substances from the systemic circulation are the urine and/or faeces (via bile and from the gastrointestinal mucosa) (ECHA 2017a). After hydrolytic degradation, UDMA is conjugated to form more water-soluble molecules that are excreted in urine or metabolized further. One of the main metabolites, methacrylic acid, will be mainly excreted as CO_2 via exhaled air.

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 8: 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 429 (2002) GLP Key study Reliability: 1 (relative humidity was 45-92% for about 10 hours during the acclimation phase; does not affect the validity of the study) A pre-test was performed in 2 mice with concentrations of 25 and 50% to determine the highest non-irritant test concentration.	CBA/CaOlaHsd female mice 4 per each treatment group, 4 in control group (vehicle only) (total n = 16)	UDMA, purity 96.99% Vehicle: dimethylformamide (DMF), purity 99% Positive control: α-hexylcinnamaldehyde (CAS 101-86-0) in acetone:olive oil (4:1)	10, 25 and 50% 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 (appr. 5 hours after treatment)	**Sensitising** The SI values at 10, 25 and 50% were 1.58, 1.70, and 4.44, respectively. EC3 value: 36.9% (w/w) Observations: no mortality occurred during the study period. No symptoms of local toxicity at the ears of the animals and no systemic findings were observed. Body weight was within normal range.	Anonymous (2009f)

Animal data:

The sensitising potential of UDMA has been investigated in one local lymph node assay (Table 8). The LLNA was conducted on mice in accordance with OECD TG 429 (2002) and principles of GLP (Anonymous 2009f). The purity of the substance was 96.99% (impurities have been taken into consideration in the resulting classification). A pre-test was performed in two animals with concentrations of 25 and 50% to determine the highest non-irritant test concentration on three consecutive days. At these concentrations, the animals did not show any signs of irritation or systemic toxicity.

In the main study, three treated groups of four CBA/CaOlaHsd female mice aged 8-12 weeks and weighing 18.6-21.3 g (mean 19.9 g ± 0.8 g) were used. The animals were treated by topical application to the dorsal surface of left and right ear lobes with test concentrations of 10, 25 and 50% (w/v) in dimethylformamide. The application volume, 25 µl, was spread over the entire dorsal surface (diameter ~ 8 mm) of left and right ear lobes once daily for three consecutive days. The control group of four mice received vehicle only. Five days after the topical application, all mice were given 250 µl of 79.9 µCi/ml ^{3}H-methyl thymidine (corresponds to 20.0 µCi ^{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 (with eight nodes per group). Single cell suspensions of

lymph node cells were prepared from the pooled lymph nodes. The proliferative capacity of the cells was determined by the incorporation of ^{3}H-methyl thymidine measured on a β-scintillation counter.

No mortality or clinical signs were observed during the study period, and the body weight of the animals remained within the normal range. A substance is regarded as a sensitiser in the LLNA if the exposure to one or more test concentration results in a three-fold or greater increase in incorporation of ^{3}H-methyl thymidine compared with vehicle-treated controls (the ratio is termed as the Stimulation Index, SI). The estimated test substance concentration required to produce an SI is referred to as the EC3 value. In this study, Stimulation Indices of 1.58, 1.70 and 4.44 were determined at concentrations of 10, 25 and 50%, respectively (Table 9). The EC3 value was 36.9% (w/w).

Table 9: Calculation of Stimulation Indices per dose group

Test item concentration % (w/v)	Group	Measurement DPM	Calculation			Result
			DPM-BG[a)]	Number of lymph nodes	DPM per lymph node[b)]	SI
-	BG I	23	-	-	-	-
-	BG II	19	-	-	-	-
0	1	6433	6412	8	801.5	1.00
10	2	10151	10130	8	1266.5	1.58
25	3	10929	10908	8	1363.5	1.70
50	4	28518	28497	8	3562.1	4.44

DPM = disintegrations per minute; BG = background (1 ml 5% trichloroacetic acid) in duplicate; 1 = control group; 2-4 = test groups; SI = Stimulation Index

a) = the mean value was taken from the figures BG I and BG II

b) = since the lymph nodes of the mice of a dose group were pooled, DPM/node was determined by dividing the measured value by the number of pooled lymph nodes

Human data

The most relevant clinical studies for UDMA, 27 in total, are presented in Table 10**. The studies comprised a total of 169 patients who tested positive to the substance. In all studies, the diagnostic method was patch testing. Data on skin exposure to UDMA is scarce.**

Table 10: 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				
Case report	UDMA (concentration and vehicle not defined)	47-year-old woman had used acrylic nails for 10 years. She presented with periungual dermatitis of all the finger nails. Symptoms had begun 6 months earlier.	She tested positive to 11 acrylic compounds including UDMA. UDMA reaction was + at 96 hours.	Paley et al. (2006)
PATIENT SERIES				
Patient	UDMA	Report of 22 patch-tested	Positive reaction to UDMA in 2	Meding &

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
series		hearing-aid users with severe dermatitis in the ear canal	(9.1%) of the patients	Ringdahl (1992)
Patient series	UDMA (0.6% and 0.2% in pet.) purity 97%	Report on 5 cases with severe skin symptoms in the fingers from photo-bonded acrylic nails at the Dermatologic and Pediatric Allergy Clinic in Wilhelminen Hospital, Vienna, Austria	Positive reaction to UDMA in 2 (40%) of the patients.	Hemmer et al. (1996)
Patch test	UDMA (2% in pet.), purity 95%	126 dental technicians were tested with (meth)acrylates in 1995-1999	3 of 126 (2.4%) patients reacted ambiguously to UDMA; no clearly positive reactions. UDMA was a common constituent of products and authors considered that the technicians had daily contact with UDMA. They considered that sensitisation was low.	Peiler et al. (2000)
Patients series	UDMA (1% in pet.)	A retrospective study of 13 833 patients tested for contact allergy at the Department of Dermatology, Catholic University (Leuven, BE) in 1978-1999	Positive reaction to UDMA in 1 of 72 (1.4%) patients who were positive to some (meth)acrylate It is unclear how many patients were tested with (meth)acrylates.	Geukens & Goossens (2001)
Patient series	UDMA (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, 6 of 20 patients (30%) reacted positively to UDMA. There were no positive reactions to the test substance in dental nurses.	Kiec-Swierczynska & Krecisz (2002)
Patient series	UDMA (2% in pet.)	27 patients in contact with artificial nails (16 nail technicians, 11 customers) tested with acrylic compounds and apparently positive to some acrylic compound at the Departments of Dermatology in Universities of Ghent and Leuven, BE)	Positive reaction to UDMA in 2 (10%) of 20 patients tested with UDMA	Constandt et al. (2005)
Patient series	UDMA (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	Positive reactions to UDMA in 3 cases: 1 dentist (+ reaction), 2 dental nurses (++ reaction and + reaction). UDMA was not mentioned in the safety data sheets of the products used by these 3 patients.	Aalto-Korte et al. (2007)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		identified.		
Patient series	UDMA (2% in pet.)	8 patients with severe skin reactions after use of a UDMA-containing UV-curing nail polish were patch tested with the components and ingredients of the nail polish at 5 dermatology departments in Sweden.	Positive reactions to UDMA in **7** patients (87.5%) All 8 patients had known exposure to UDMA.	Dahlin et al. (2016)
Patient series	UDMA (2% in pet.)	A retrospective study on 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	A total of 2353 patients were patch tested during the study period. 43 (1.82%) were diagnosed with ACD due to (meth)acrylates in long lasting nail polish. In this group, positive reaction to UDMA in 6 of 36 (16.7%) patients tested with UDMA	Gatica-Ortega et al. (2017)
Patients series	UDMA (Chemotechnique's or Trolab's test substance i.e. 2% in pet.)	A retrospective study of the European Environmental Contact Dermatitis Research Group (EECDRG) on allergic contact dermatitis from (meth)acrylates due to artificial nails diagnosed in 11 clinics in 9 European countries in 2013-15	A total of 202 patients were positive to some acrylic compound and 10 (2.0%) were positive to UDMA. It is not clear how many patients were tested with UDMA.	Gonçalo et al. (2018)
Patient series	UDMA (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	208 patients 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 reactions to UDMA in 6 of 26 (23.1%) patients tested with the substance.	Marrero-Alemán et al. (2019)
Patient series	UDMA (2%; AllergEAZE's test substance, i.e. in pet.)	A retrospective study on 156 patch-tested patients with a profession associated with - cosmetic nail procedures or use of such services at the Department of Dermatology and Venereology, Athens, GR in 2014-2018	37 (23.7%) patients were positive to UDMA 116 patients had positive reactions to some (meth)acrylate. The UDMA-positive cases constituted 31.9% of these.	Gregoriou et al. (2020)
CROSS-SECTIONAL STUDIES				
Cross-sectional study	UDMA (2% in pet.)	A questionnaire was sent to 1132 dental technicians and 173 answered. 55 cases were patch tested.	UDMA was positive in 1 (2%) case with hand dermatitis	Rustemeyer & Frosch (1996)
Cross-sectional	UDMA (2%, Chemotechnique's test substances i.e.	A questionnaire was sent to 3500 Swedish dentists and 1287 answered. 191 with	UDMA was positive in 2 (1.4%) patients	Wallenhammar et al. (2000)

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
study	in pet.)	hand eczema were invited to patch tests and 147 attended.		
Cross-sectional study	UDMA (Chemotechnique's test substance i.e. 2% in pet.)	49 out of 1038 dental technicians voluntarily participated a study on patch testing at the Department of Dermatology in the Catholic University of Korea, Soeul, Korea.	Positive reaction to UDMA in 1 case, 2.1% of those tested. 7 patients were positive to some acrylic substance. The UDMA positive case constituted 14% of this group.	Lee et al. (2001)
CLINICAL PATCH TEST DATA ON SELECTED PATIENTS (AIMED TESTING WITH ACRYLIC COMPOUNDS); Frequency of positive reactions among tested individuals given				
Patch test data, selected patients	UDMA (2%, Chemotechnique's test substance i.e. in pet.)	A retrospective study on patients tested with (meth)acrylate patch test series at the Section of Dermatology in the Finnish Institute of Occupational Heath in 1985-1995	Positive reaction to UDMA in 1 (0.4%) of 273 patients tested with UDMA. 48 patients reacted positively to some (meth)acrylate. The UDMA-positive case constituted 2% of these.	Kanerva et al. (1997)
Patch test data, selected patients	UDMA (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 UDMA in 2 of 268 (0.7%) patients tested with UDMA	Tucker & Beck (1999)
Patch test data, selected patients	UDMA (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	9 (0.4%) allergic reactions to UDMA in 2408 patients tested. The frequency of allergic reactions varied between 0.0% and 1.5% in different clinics.	Kanerva et al. (2001)
Patch test data, selected patients	UDMA (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 UDMA in 2 (1.8%) of 109 patients tested with (meth)acrylates 24 patients had allergic reactions to some (meth)acrylate. The 2 UDMA-positive cases constituted 8.3% of these	Wrangsjö et al. (2001)
Patch test data, selected patients	UDMA (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 UDMA in 1 (0.06%) of 1632 patients tested 48 patients reacted positively to at least one (meth)acrylate. The UDMA-positive case constituted 2.1% of these.	Goon et al. (2006)
Patch test data, selected	UDMA (2% in pet.)	A retrospective study on 451 patients suspected of having occupational contact	Positive reactions to UDMA in 5 (1.1%) of the patients tested. 66 patients reacted positively to at	Aalto-Korte et al. (2010) Includes the

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
patients		dermatitis and tested with a (meth)acrylate series at Finnish Institute of Occupational Health (Helsinki, FI) in 1994-2009	least one (meth)acrylate. Positive reaction to UDMA in 5 (7.6%) of these 66 patients	patients in Aalto-Korte et al. (2007)
Patch test data, selected patients	UDMA (2%; Chemotechnique's test substance i.e. in pet.)	A retrospective study on patients tested with a (meth)acrylate series at the Department of Dermatology, University Medical Centre in Groningen (NL) in 1993-2012	Positive reactions in 4 of 151 (2.6%) patients tested with UDMA. 24 patients reacted positively to some (meth)acrylate. The positive reactions to UDMA constituted 16.7% of these.	Christoffers et al. (2013)
Patch test data, selected patients	UDMA (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 UDMA in **7** patients, 5.7% of 122 tested. 37 patients reacted positively to (meth)acrylates. The UDMA-positive cases constituted 18.9% of these.	Ramos et al. (2014)
Patch test data, selected patients	UDMA (vehicle and concentration not stated)	6775 patients were tested with a series intended for dental technicians with occupational dermatitis. UDMA was included in this series. The patch tests were performed in dermatology clinics of the IVDK network in German-speaking countries in 2008−2015.	47 patients tested positive to UDMA (0.7% of 6775 patients tested). UDMA was the least frequent allergen among the (meth)acrylates in this series.	Geier & Schnuch (2016)
Patch test data, selected patients	UDMA (2% in pet.)	475 patients were tested with a series of (meth)acrylates at the Cutaneous Allergy Unit (Birmingham, UK) in 2002-2015	Positive reactions to UDMA in 6 (1.3%) patients tested with UDMA. 52 patients reacted positively to (meth)acrylates. The positive reactions to UDMA constituted 11.5% of these.	Spencer et al. (2016)
Patch test data, selected patients	UDMA 2% (vehicle not stated; FIRMA Diagent allergen)	A prospective study on screening contact allergy to acrylic acid on consecutively patch-tested patients in 3 Italian patch test clinics in January-March 2018. Additional patch tests with a (meth)acrylate series were performed in patients positive to acrylic acid or 2-hydroxyethyl methacrylate or with a history of (meth)acrylate allergy	The study comprised a total of 436 consecutive patients. 30 patients were tested with (meth)acrylates including UDMA. Positive reaction in 1 patient (3.3% of those tested)	Hansel et al. (2020)

Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and is performed according to international standards by dermatologists (Johansen et al. 2015). The results of such tests are usually reported as number of patients/subjects with positive reactions in relation to the total number of

tested (frequency of positive patch tests). An important factor of assessing prevalence of positive reactions in diagnostic patch test is how the group of patients is defined, i.e. if they are selected 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 UDMA in general population or unselected dermatitis patients.

UDMA is usually tested as part of (meth)acrylate patch test series, and it has been commonly tested since the 1980s. Its established test concentration is 2% in petrolatum. A total of 11 studies on diagnostic patch testing in selected patients could be identified for UDMA. The frequency of positive reactions varied between 0.06% and 5.7% (median 1.1%). The lowest frequencies were seen in earlier reports from clinics investigating general dermatology patients.

No strict workplace studies could be identified for UDMA. However, three cross-sectional studies on risk occupations share a similar design. The risk occupations for contact allergy to acrylic compounds were dentists in one study and dental technicians in two studies (Rustemeyer & Frosch 1996, Wallenhammar et al. 2000, Lee et al. 2001). Workers with skin symptoms suggesting possible contact allergy (hand dermatitis, for instance) were patch tested. Frequency of positive patch test reactions to UDMA varied between 1.4% and 2.1% in tested individuals.

The rest of the identified studies were either case reports (one report of a single case) or reports describing patient series without clearly stating the frequency of reaction to UDMA in all patients tested with the substance during the same time period. The number of patients in these ten reports were between 5 and 202, and the groups comprised for instance patients sensitised to some acrylate or methacrylate. The frequency of positive reactions to UDMA within these patient groups varied between 0% and 88% of patients tested with the substance. The highest frequency was in a report of eight cases who had developed severe skin symptoms while using a UDMA-containing UV-cured nail polish (Dahlin et al. 2016). On patch testing, seven of the patients had allergic reactions to UDMA. The remaining patient developed no contact allergy. In contrast to this finding, Peiler et al. (2000) patch tested 126 dental technicians with daily contact with UDMA-containing products, and found no clearly positive reactions to UDMA. The authors considered that sensitisation was low. Dental technicians' skin exposure to UDMA may vary within countries; for instance in Finland only one dental technician out of eight had used UDMA-based products (Aalto-Korte et al. 2007).

Table 11: 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

The sensitising potential of UDMA has been investigated in one local lymph node assay (Table 8). The LLNA was conducted on mice in accordance with OECD TG 429 (2002) and principles of GLP (Anonymous 2009f). A pre-test was performed in two animals with concentrations of 25 and 50% to determine the highest non-irritant test concentration on three consecutive days. At these concentrations, the animals did not show any signs of irritation or systemic toxicity. In the main study, three treated groups of four mice were treated with test concentrations of 10, 25 and 50% (w/v) topically in dimethylformamide. No mortality or clinical signs were observed during the study period, and the body weight of the animals remained within the normal range. A dose-related increase in the stimulation index (SI) values was observed and the threshold positive value of 3 was exceeded at 50% concentration.

In humans, a total of 27 clinical patch test studies were identified for UDMA, with 11 of them in selected patients. There are no studies in general population or in unselected dermatitis patients. The frequency of positive reactions varied between 0.06% and 5.7% (median 1.1%). Dentist and dental technician are identified as risk occupations for contact allergy following exposure to acrylic compounds, such as UDMA.

All the remaining studies were either single case reports or reports describing patient series without clearly stating the frequency of reaction to UDMA.

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 principles of GLP), UDMA showed an EC3 value of 36.9% (w/w), 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 result allows classification in Sub-category 1B.

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**	**UDMA**
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 0.06% − 5.7% (median 1.1%)
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 (3 cross-sectional studies; 1.4% −2.1%)
Number of published cases	≥ 100 cases	< 100 cases	169 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 around the limit of high frequency (0.06% − 5.7%; median 1.1%).

In three cross-sectional studies on risk occupations (mimicking workplace studies) the frequencies of positive patch tests were between 1.4% and 2.1%, i.e. above the limit. Not all or randomly selected workers but those with skin symptoms were patch tested in these studies.

The number of published patch-test-positive cases, 169, exceeds the limit for high frequency.

Positive patch test reactions to UDMA are not extremely rare in patients sensitised to methacrylates, but specific exposure to the substance in sensitised patients or patients tested has rarely been described in the literature. Both the exposure and the lack of exposure to UDMA are typically difficult to assess in clinical work due to the unavailability of chemical analyses. Positive reactions may also arise from cross-reactivity to other methacrylates, yet true exposure to UDMA in clinical patients cannot be excluded. The only study confirming exposure to UDMA is by Dahlin et al. (2016) that describes a series of eight patients with severe skin symptoms due to use of a UV-cured nail polish containing 2-hydroxyethyl methacrylate (HEMA) and UDMA. Seven of these patients tested positive to UDMA (87.5%).

To conclude, the frequency of positive reactions to UDMA in diagnostic patch tests can be considered high. However, there is no adequate information enabling the assessment of true exposure to the substance. Based on the available animal data, i.e. the key LLNA, sub-categorization is warranted. As Sub-category 1A can be excluded, Sub-category 1B can be applied instead of Category 1 (ECHA 2017b). Human data supports the classification of UDMA as a skin sensitiser.

10.7.3 Conclusion on classification and labelling for skin sensitisation

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

10.8 Germ cell mutagenicity

Not assessed in this dossier.

10.9 Carcinogenicity

Not assessed in this dossier.

10.10 Reproductive toxicity

Not assessed in this dossier.

10.11 Specific target organ toxicity-single exposure

Not assessed in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Not assessed in this dossier.

10.13 Aspiration hazard

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Not assessed in this dossier.

11.2 Environmental transformation of metals or inorganic metals compounds

Not assessed in this dossier.

11.3 Environmental fate and other relevant information

Not assessed in this dossier.

11.4 Bioaccumulation

Not assessed in this dossier.

11.5 Acute aquatic hazard

Not assessed in this dossier.

11.6 Long-term aquatic hazard

Not assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Not assessed in this dossier.

13 ADDITIONAL LABELLING

The label on the packaging of mixtures not classified as sensitising but containing UDMA, 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 impurity