Scientific Committee on Consumer Safety

SCCS

OPINION ON

the safety of cosmetic ingredients HEMA and Di-HEMA Trimethylhexyl Dicarbamate

Submission I

(Sensitisation only)

The SCCS adopted this Opinion at its plenary meeting on 21-22 June 2018

ACKNOWLEDGMENTS

SCCS members listed below are acknowledged for their valuable contribution to the finalisation of this Opinion.

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All Declarations of Working Group members are available on the following webpage:
http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

This Opinion has been subject to a commenting period of a minimum eight weeks after its initial publication (from 22 December 2017 until 26 February 2018). Comments received during this time were considered by the SCCS.
For this Opinion, comments received resulted mainly in the following changes: *sections 3.3.11 human data and discussion part on sensitisation, as well as the 2nd conclusion on scientific concerns.*

1. ABSTRACT

The SCCS concludes the following:

1. In light of the data provided, does the SCCS consider monomers of HEMA and Di-HEMA Trimethylhexyl Dicarbamate, safe at concentrations of up to 35% and 99% respectively when used in topically applied UV-cured artificial nail modelling systems?

The available evidence suggests that normal nail plate acts as a good barrier to penetration of chemical substances in general, and that both methacrylate monomers (HEMA and di-HEMA-TMHDC) polymerise rapidly under UV curing when applied as part of an artificial nail modelling system. This leaves very little chance for the monomers to be absorbed in any appreciable amount through the nail plate. In view of this, the SCCS is of the opinion that HEMA and di-HEMA-TMHDC, when applied appropriately to the nail plate at concentrations of up to 35% and 99% respectively as part of an artificial nail modelling system, are not likely to pose a risk of sensitisation, provided that their use is restricted to the nail plate only and contact with the adjacent skin is avoided.

2. Does the SCCS have any further scientific concerns with regard to the use of HEMA and Di-HEMA Trimethylhexyl Dicarbamate monomers in cosmetic products?

- More analytical data are needed to exclude the possibility of the presence of other sensitisers that may be present as impurities or degradation products alongside the two methacrylate monomers.
- Both HEMA and di-HEMA-TMHDC are weak to moderate sensitisers and pose a risk of sensitisation from misuse of the products or from inappropriately carried out application or from unintentional contamination of the skin adjacent to the nails under normal and reasonably foreseeable conditions of use.
- Filing or sanding nails to remove/replace previous applications may generate particle dust that may lead to respiratory exposure of the professionals if appropriate protective measures are not in place.
- The potential for sensitisation to the methacrylate monomers is likely to be higher amongst the professionals who carry out routine applications of artificial nail modelling systems without appropriate protective measures.
- In view of the growing popularity of artificial nail fashions and the potential use by consumers at home, and considering the observations of several professional dermatological organisations that the prevalence of contact dermatitis from artificial nail products (among which HEMA is an important constituent) is rising, a further increase of the prevalence of sensitisation is possible.

Keywords: SCCS, scientific opinion, cosmetic ingredients, 2-hydroxyethyl methacrylate HEMA (CAS 868-77-9 and EC 212-782-2), Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4 and EC 276-957-5), SCCS/1592/17, Regulation 1223/2009

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These Committees are the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and are made up of scientists appointed in their personal capacity.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

TABLE OF CONTENTS

2. BACKGROUND

The cosmetic ingredients HEMA, with chemical name 2-hydroxyethyl methacrylate (CAS 868-77-9, EC 212-782-2), and Di-HEMA Trimethylhexyl Dicarbamate, with chemical name 7,7,9 (or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate (CAS 41137-60-4/72869-86-4, EC -/276-957-5) are active components of topically applied artificial nail modelling systems cured by ultraviolet (UV) light. The methacrylate ester monomers HEMA and Di-HEMA Trimethylhexyl Dicarbamate are used as film forming ingredients in nail products, where they are consumed within a few seconds to minutes during the polymerization induced by the UV-curing process.

In August 2014, the Commission was informed of a decision of the Swedish authorities to withdraw and prohibit the sale and delivery of a range of nail polishes, according to Article 27 (Safeguard clause) of Regulation (EC) No 1223/2009 on cosmetic products. These products were notified through the RAPEX system, pursuant to Article 12 of Directive 2001/95/EC on general product safety, as posing a serious risk to consumers (RAPEX notification A12/1226/14).

The Swedish authorities consider that the above-mentioned products, which are hardened with the use of a LED lamp after application, constitute a serious risk for consumers as they can lead to contact allergy and result in damage to nails and/or hands. Available scientific evidences suggest that the sensitising potential could be related to the uncured (not fully reacted), unpolymerised reactive monomers HEMA and Di-HEMA Trimethylhexyl Dicarbamate.

In 2016, the Commission launched a public call for data to retrieve safety information on HEMA, Di-HEMA Trimethylhexyl Dicarbamate and in addition on the class of compounds termed "urethane acrylates".

Following this call for data, several contributions from Member States' national authorities, clinicians and industry experts have been submitted to the Commission services.

The two substances Di-HEMA Trimethylhexyl Dicarbamate and HEMA are used as cosmetics ingredients and listed in CosIng, the European Commission database for cosmetic ingredients, while "urethane acrylates" indicates a class of substances that is not registered in CosIng as such. Further clarifications are needed on the specific substances of this class that are used as cosmetic ingredients and that could represent a concern for consumer safety. Therefore the scope of this current safety evaluation is limited to the monomers of HEMA and Di-HEMA Trimethylhexyl Dicarbamate.

3. TERMS OF REFERENCE

1. In light of the data provided, does the SCCS consider monomers of HEMA and Di-HEMA Trimethylhexyl Dicarbamate, safe at concentrations of up to 35 % and 99% respectively when used in topically applied UV-cured artificial nail modelling systems?

2. Does the SCCS have any further scientific concerns with regard to the use of HEMA and Di-HEMA Trimethylhexyl Dicarbamate monomers in cosmetic products?

4. OPINION

4.1 Chemical and Physical Specifications

4.1.1 Chemical identity

4.1.1.1 Primary name and/or INCI name

INCI names: HEMA and Di-HEMA TRIMETHYLHEXYL DICARBAMATE

4.1.1.2 Chemical names

HEMA

Chemical name: 2-Hydroxyethyl methacrylate
IUPAC name: 2-Hydroxyethyl methacrylate

Di-HEMA Trimethylhexyl Dicarbamate

Chemical name: Di-HEMA trimethylhexyl dicarbamate
IUPAC name: 11,14-Dioxa-2,9-diazaheptadec-16-enoic Acid, 4,4,6,16-tetramethyl-10,15-dioxo,2-[(2-methyl-1-oxo-2-propenyl)oxy]ethyl ester

Ref: CosIng

4.1.1.3 Trade names and abbreviations

HEMA

2-HEMA
2-Hydroxyethyl ester, methacrylic acid
Ethylene glycol methacrylate
HEMA
Hydroxyethyl methacrylate

Di-HEMA Trimethylhexyl Dicarbamate

Depositor-Supplied Synonyms:
Urethane dimethacrylate
2-Propenoic acid, 2-methyl-, 7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl ester
7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate
11,14-Dioxa-2,9-diazaheptadec-16-enoic acid, 4,4,6,16-tetramethyl-10,15-dioxo-, 2-((2-methyl-1-oxo-2-propen-1-yl)oxy)ethyl ester
11,14-Dioxa-2,9-diazaheptadec-16-enoic acid, 4,4,6,16-tetramethyl-10,15-dioxo-, 2-((2-methyl-1-oxo-2-propenyl)oxy)ethyl ester
11,14-Dioxa-2,9-diazaheptadec-16-enoic acid, 4,4,6,16-tetramethyl-10,15-dioxo-, 2-[(2-methyl-1-oxo-2-propenyl)oxy]ethyl ester
CCRIS 8223

MeSH Entry Terms:
1,6-di-(methacryloxy-2-ethoxycarbonylamino)-3,5,5-trimethylhexane
Lumin-X
Opalux
UDMA compound
urethane dimethacrylate
urethane dimethacrylate luting resin
urethane-di-methacrylate
Visioform

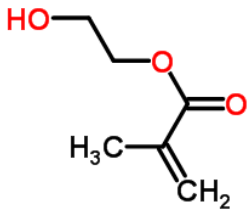
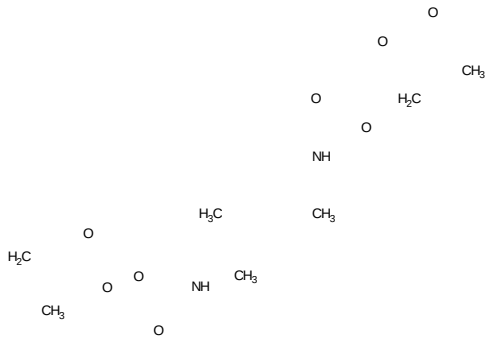
Ref: PubChem: https://pubchem.ncbi.nlm.nih.gov/compound/170472#section=Synonyms, CIR, 2005; OECD SIDS, 2001

4.1.1.4 CAS / EC number

HEMA:
CAS: 868-77-9
EC: 212-782-2

Di-HEMA Trimethylhexyl Dicarbamate:
CAS: 41137-60-4, 72869-86-4
EC: 276-957-5

4.1.1.5 Structural formula

	
HEMA	Di-HEMA Trimethylhexyl Dicarbamate

Ref: ChemSpider, PubChem

4.1.1.6 Empirical formula

Formula HEMA: $C_6H_{10}O_3$
Formula Di-HEMA: $C_{23}H_{38}N_2O_8$

4.1.2 Physical form

Physical form HEMA: Clear liquid

4.1.3 Molecular weight

Molecular weight HEMA: 130.14 g/mol
Molecular weight Di-HEMA: 470.56 g/mol

4.1.4 Purity, composition and substance codes

HEMA:
Purity: 97.0 - >99%

SCCS comment
Additional information on the analytical method used to evaluate peak purity is needed. Data on the purity of Di-HEMA Trimethylhexyl Dicarbamate was not provided.

4.1.5 Impurities / accompanying contaminants

HEMA:
Diethylene glycol mono-methacrylate: < 2.0%
Ethylene glycol di-methacrylate: < 0.2%
Water: < 0.04%
Methacrylic acid: < 0.04%
Ethylene oxide: < 0.001%
4-Methoxy phenol (syn. Hydroquinone Methylether (MeHQ)): 40 – 80 ppm (additive for prevention of polymer formation). Noteworthy to mention that in commercial nail products for professional and for non-professional use, the MeHQ content will be at maximum 200 ppm and thus in line with the current cosmetics regulation.

SCCS comments
Additional information on the analytical method used for the chemical characterisation of impurities is needed. Data on the impurities of Di-HEMA Trimethylhexyl Dicarbamate have not been provided.

4.1.6 Solubility

HEMA:
Water solubility: Miscible with water and soluble in common organic solvents

(PubChem reference: Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 12th ed. New York, NY: Van Nostrand Rheinhold Co., 1993, p. 622)

Di-HEMA Trimethylhexyl Dicarbamate:
Soluble in water: 30 mg/L at 37 °C (experimental, ChemIdPlus)

Reference: OECD SIDS, 2001; Keystone, 2016

4.1.7 Partition coefficient (Log Pow)

HEMA:
Log Pow: measured: 0.42 at 25 °C and pH ≥ 5.9 – ≤ 6.1 (OECD 107)

DI-HEMA Trimethylhexyl Dicarbamate:
LogPow = 4.69 (estimated, ChemIdPlus)

4.1.8 Additional physical and chemical specifications

HEMA
Melting point: -12 °C (experimental, Alfa Aesar, ChemSpider)
Boiling point: 250 °C (experimental, Alfa Aesar, ChemSpider)
Flash point: 101 °C (experimental, Alfa Aesar, ChemSpider)
Density: 1.1±0.1 g/cm^3 (predicted, ACD/Labs, ChemSpider)
Vapour pressure: 0.2±0.7 mmHg at 25°C (predicted, ACD/Labs, ChemSpider)
Viscosity: /
pKa: /
Refractive index: 1.453 (experimental, Alfa Aesar, ChemSpider)
UV_Vis spectrum: /

Di-HEMA Trimethylhexyl Dicarbamate (Di-HEMA-TMHDC):
Melting point: /
Boiling point: 594.3±45.0 °C at 760 mmHg (predicted, ACD/Labs, ChemSpider)
Flash point: 313.2±28.7 °C (predicted, ACD/Labs, ChemSpider)
Vapour pressure: 0.0±1.7 mmHg at 25°C (predicted, ACD/Labs, ChemSpider)
Density: 1.1±0.1 g/cm^3 (predicted, ACD/Labs, ChemSpider)
Viscosity: /
Surface Tension: 37.6±3.0 dyne/cm (predicted, ACD/Labs, ChemSpider)
pKa: /
Refractive index: 1.479 (predicted, ACD/Labs, ChemSpider)
Molar Refractivity: 122.0±0.3 cm^3 (predicted, ACD/Labs, ChemSpider)
UV_Vis spectrum: /

Ref: www.chemspider.com

4.1.9 Homogeneity and Stability

HEMA:
The product is stable

Ref: Keystone, 2016

SCCS comment
Additional information on the stability studies (conditions, any stabiliser added, analytical method used to evaluate stability) is not provided. Data on the stability of Di-HEMA Trimethylhexyl Dicarbamate are also not provided.

Polymerisation

The polymerization of 22 methacrylates including HEMA was measured in an ethyl methacrylate based system using Differential Scanning Calorimetry (DSC). Maximum peak exotherm and total exotherm were measured as indications for the polymerization process, while the nail enhancement product reacted in the test chamber. Maximum peak exotherm occurs at gelation (gel point) of a curing nail enhancement system. The gelation point is reached when at least 50% of the monomer has reacted and the material has a hardened surface. This process starts immediately and takes 2 to 4 minutes in most commercially available professional monomer-based nail enhancement systems. Changes in gel point time and total exotherm are both directly proportional to the test monomers' reactivity.

In the experiment, the Radical® artificial nail monomer/polymer system was modified by adding 5% ethyl methacrylate to establish a normalised baseline to compare reactivity of various test monomers including HEMA. Each of the 22 test monomers were added at a concentration of 5% and 50% (by weight) to the Radical® artificial nail monomer/polymer system.

The results show that polymerization of HEMA was fast in general and even faster at a higher concentration (Table 1). This can be considered as an indication of strong reactivity.

Table 1. Results of differential scanning calorimetry regarding HEMA in nail product

HEMA concentration	5%	50%
Polymerization set time	2.85 ± 5.0 min	1.82 ± 1.0 min
Total exotherm	672.07 ± 4.4 mJ/m²	1130.3 ± 6.3 mJ/m²

Ref: Creative Nail Design, 2001; Schoon, 1994a +b

Extraction

Explorative analytical screening investigations to mimic use conditions are available. The amount of extractable Hydroxyethyl Methacrylate (HEMA) amongst other methacrylates from cured films of UV/LED full coat system, an acrylic and a builder system, applied on a glass slide, was analysed using a 0.1% salt water solution or acetone as extraction solvent.

The salt water extracts were analysed by High Performance Liquid Chromatography (HPLC) and the acetone extracts were analysed by Gas Chromatography (GC).

The HEMA containing samples were prepared as follows:

Preparation of Samples

NC6195M: Base coat was applied to a glass slide using a 5 mil drawdown bar and cured for 3 minutes in Young Nails UV lamp. The first colour coat was applied to the glass slide using a 10 mil drawdown bar and cured for 3 minutes. The second colour coat was applied to the glass slide using a 15 mil drawdown bar and cured for 3 minutes. The top coat was applied using a 20 mil drawdown bar and then cured for 3 minutes. The surface was then wiped with isopropyl alcohol. The slide was left to sit at room temperature for 72 hours.

NC6195N: Base coat was applied to a glass slide using a 5 mil drawdown bar and cured for 1 minute in OPI Studio LED lamp. The first colour coat was applied to the glass slide using a 10 mil drawdown bar and cured for 1 minute. The second colour coat was applied to the glass slide using a 15 mil drawdown bar and cured for 1 minute. The top coat was applied using a 20 mil drawdown bar and then cured for 1 minute. The surface was then wiped with isopropyl alcohol. The slide was left to sit at room temperature for 72 hours.

NC61950-1 & -2: A nail brush was dipped in J2 monomer to wet it. The brush was then dipped into P3 acrylic powder. The wet powder was then applied to a glass slide and left to sit at room temperature for 72 hours. Thereafter, the cured film was scraped off the glass slide and transferred to a glass vial. The weight of the cured film was recorded. The salt water solution was added to one of the duplicate samples and acetone was added to the other. The samples were allowed to extract at room temperature for approximately 24 hours. Then, the salt water solution extracts were analysed on an Agilent 1290 HPLC with a diode array detector and the acetone extracts were analysed on an Agilent 6890 GC with an FID detector.
All HPLC and GC system suitability requirements were met. The detector response to concentration was linear for the range tested in all standards. The limit of detection (LOD) was 1.0 ppm for both the HPLC and GC analysis.

Table 2. HEMA Extraction Results

Sample	Light source	Cure Time	Sample Description	Theoretical HEMA Uncured	Extracted HEMA in salt water	Extracted HEMA in Acetone
NC-6195M	UV	3 minute	Full Coat system#	10-25 %	2892 ppm or 0.2892 %	2994 ppm or 0.2994 %
NC-6195N	LED	1 Minute	Full Coat system#	10-25 %	4027 ppm or 0.4027 %	4854 ppm or 0.4854 %
NC-61950-1	N/A	N/A	Acrylic Powder and monomer	1-5 %	3803 ppm or 0.3803 %	N/A
NC-61950-2	N/A	N/A	Acrylic Powder and monomer	1-5 %	4867 ppm or 0.4867 %	N/A
# A full coat system includes a base coat, two color coats and a top coat. N/A = not applicable						

There was no significant difference between the curing time, the light source, the applied product or the extraction medium, when normal analytical variation was considered. Curing for 1 min using LED light resulted in a comparable extractable amount of HEMA compared to 3 min curing under UV light. Even following a hardening process without artificial light exposure led to a comparable amount of extractable HEMA.
In any case the extractable HEMA portions were in the same order of magnitude and ranged between 0.28 % – 0.49 % using salt water and between 0.3 % – 0.49 % with acetone as extraction medium (Reference: Steffier, 2016).
However, these explorative analytical screening data represent a worst case situation and should therefore not be used for general regulatory purposes, e.g., not to fix specific limit values.

SCCS comment
Information on the speed and completeness of the polymerisation and extraction of Di-HEMA-TMHDC monomer under use conditions along with information on the concentration and the type of polymerisation inhibitor and polymerisation activator is not provided. Information on various commercial systems used for polymerising HEMA and DiHEMA-TMHDC is also not provided.

4.2 Function and uses

From the submission:
The HEMA monomer is a methacrylate ester and is used in nail products to form a film. In principle, two major processing systems for nail modelling systems are available, two

component powder/liquid systems (self- or light curing) and light-curing single component gel systems (composites). The current and anticipated use concentrations of HEMA are up to 10% in powder/liquid systems and up to 35% in gel systems. The artificial nail modelling systems are used for fingernails- and toenails.
HEMA will be consumed rapidly during the polymerisation process (within 1.82 minutes). Explorative screening investigations showed that under worst-case conditions, the extractable monomer portion is at maximum in the order of about 0.49 % (4900 ppm).
For both nail modelling systems, quantities of 2 to 4 g are used for the first application and approximately 1 g for filling up after approximately 2 to 3 weeks, corresponding to a maximum of 1400 mg HEMA in total for all nail plates. Contact is meant to be limited to the keratin of the nail plate.
Clear use instructions and adequate training of professional users should ensure that these nail products are properly applied, i.e. exclusively to the nail plate and not to the surrounding skin by ensuring a small space between the cuticle and the nail. Thus, there is no contact to skin when carefully applied to the nail plate. In case of unintended skin contact at the cuticle and the side of the nails, the use instructions call for removing it immediately from the skin, especially prior to radiation.
For the two-component systems the curing reaction is triggered by mixing the liquid and the powder. Since the reaction starts immediately and is completed after a maximum of 2 to 3 minutes, processing possibilities are limited in time. The reaction occurs with heating and odour development.
For the light-curing gel systems, which represent a further development of the composites from dental medicine, curing is started after the decomposition of the added photo initiators, and the actual curing process is already completed after 30 to 45 seconds. In practice there is, however, a curing period of 2 to 3 minutes in order to ensure optimum strength and adhesion of the nail.
For the application of the systems there are detailed descriptions, which are selectively intended to ensure not only optimum application of the nail modelling but also the highest possible protection of the users.
The application of the liquid/powder systems is carried out by means of a special brush, frequently using a template. With the tip of the brush previously immersed in the liquid, the powder is absorbed in a slight circulating movement. This forms a wax-like bead. These and possibly other beads are placed in the centre of the nail and modelled into a slight so-called C curve. The material thickness is selected in such a way that the entire nail modelling has at the so-called stress point a maximum height of 1 mm. For the gel systems the principle is similar, whereby curing by UV light is carried out between the different work steps (gel applications).
Filing is then used to optimise the form, polish and in most cases an additional top coat is applied to bring about optimum gloss. If necessary, a filling up of the acrylic modelling is carried out after a few weeks.

Ref: Creative Nail Design, 2001; Schoon, 1994a+b, Creative Nail Design, 2013, IKW, 2016

4.3 Toxicological evaluation

4.3.1 Acute toxicity

/

4.3.2 Irritation and corrosivity

/

4.3.3 Skin sensitisation

Guinea pig maximisation tests (GMPT)

A GMPT (Clemmensen 1985) investigated the influence of concentration, vehicle, and cyclophosphamide on the skin sensitising potential of HEMA. The vehicles used for elicitation were petrolatum, soybean oil, and a mixture of soybean oil and 2-butanone (sbomek). Ten to twenty guinea pigs (Scc:AL) were used per dose group. The following materials were used for intradermal induction (day 0): 1% HEMA (in soybean oil), 25% HEMA (in soybean oil), 25% HEMA (in sbomek), 1% HEMA (aqueous), 10% HEMA (aqueous), and 25% HEMA (aqueous). Dermal induction was performed on days 7 and 8 using a 10% sodium lauryl sulfate pre-treatment and 400 µl of HEMA applied via a 48 h patch. Challenge was performed on day 21 using 25% HEMA (in petrolatum), 25% HEMA (aqueous), 25% HEMA (sbomek), 25% HEMA (in soybean oil), and 100% HEMA. Effects were scored at 48 h and 72 h post-challenge.
The major determining factor for sensitisation was the concentration used for intradermal induction. Induction with 10% HEMA or greater caused a reaction in 4 to 10 guinea pigs out of 12 challenged per dose group.
There was no challenge response to challenge when an intradermal injection had been given with 1% HEMA in soybean oil. When HEMA was used at concentrations of 25 % or higher, the vehicles did not influence the response.

Other guinea pig studies showed (Katsuno 1995, Katsuno 1996) that HEMA produced positive delayed hypersensitivity reactions: 6 out of 10 albino guinea pigs induced and challenged with HEMA (100%) showed a positive reaction at 24 hours and 5 out of 10 showed a positive reaction at 48 hours.
The optimum concentration of HEMA for sensitisation and elicitation was established by testing HEMA at 0.01, 0.02, 0.1, 0.2, 0.5, 1.0, and 5.0%. Challenge concentrations were 10, 25, 50, and 100%.
It was shown that the optimum concentration to induce sensitisation was 0.2%; five of five guinea pigs had a positive challenge reaction to HEMA at 24 hours and 48 hours after patch removal with a mean skin response of 5.0 (Katsuno, 1996).

In an unpublished report (Roehm 1982, cited in OECD-SIDS 2001), HEMA was negative in the Buehler test when tested undiluted under occlusive conditions.

A study (Van der Walle 1982) with 8 albino female guinea pigs of the Himalayan white spotted outbred strain investigated the skin sensitisation potential of HEMA in a Freund's Complete Adjuvant Test (FCAT). Four guinea pigs were positive to HEMA on day 21 but all animals were negative on day 35 .

Cross-reactivity patterns of methacrylates including HEMA were studied in guinea pigs using a Freund's Complete Adjuvant Test (FCAT) (Rustemeyer 1998). HEMA led to strong cross-reactions to all other methacrylates [methacrylate (MMA), 2-hydroxypropyl methacrylate (2-HPMA) and ethyleneglycol dimethacrylate (EGDMA)], while cross-reactions to Ethylene Glycol Dimethacrylate were weak. Hydroxypropyl Methacrylate had only weak to moderate cross reactivity with HEMA.

Local lymph node assay (LLNA) on Di-HEMA-TMTDC)

Guideline/method: OECD 429
Species/strain: Mouse/CBA
Group size: 4 females per group
Test substance: Di-HEMA-TMHDC (referred to as UDMA)

Batch:	81106228 (purity: 96.99%)
Vehicle:	Dimethylformamide (DMF)
Concentrations:	0, 10, 25, 50%
Positive control:	hexyl cinnamic aldehyde
Route:	Epidermal (topical) application on the surface of the dorsal ear lobe
GLP:	Yes
Published:	No
Remark:	The study is currently in a negotiation process.

The sensitising potential of Di-HEMA-TMHDC was tested at concentrations of 10, 25 and 50% (w/w) solution in DMF (dimethylformamide). The 50% concentration was the highest non-irritant test concentration which did not show any signs of irritation or systemic toxicity up to day 8 after three-day exposure to two animals. The application volume 25 µL was spread over the dorsal surface of the ear lobes once daily for three consecutive days. Five days after the first application, all mice were intravenously injected with 250 µL of [^{3}H]-thymidine.

Results
Stimulation Indices (SIs) of 1.58, 1.70 and 4.44 were determined at concentrations of 10, 25, and 50% (w/w) in DMF, respectively. A clear dose response was observed. Based on the SI values, an EC3 value of 36.9% was calculated. A statistically significant increase in the DPM values was observed in all dose groups in comparison to the vehicle control group.
Based on the calculated EC3 value, Di-HEMA-TMTDC was, under the condition of this LLNA, considered as a weak sensitiser.

Ref: information taken from the submission

SCCS comment on the animal studies
Studies in guinea pigs:
While for most studies it is unclear whether the OECD guidelines were followed, induction of sensitisation was achieved in a number of tests with injection of Freund's adjuvant. Although guinea pig tests are not suitable to establish potency, the available data point toward HEMA being a moderate skin sensitiser.

LLNA
HEMA was not tested in the LLNA. Therefore, no information on the skin sensitising potency is available.
The LLNA with Di-HEMA-TMHDC indicates that it is a weak sensitiser.

4.3.4 Dermal / percutaneous absorption

From the submission dossier
There is no dermal penetration study available for HEMA.
However, exposure to HEMA is negligible when adhering to proper use conditions, i.e. no contact to skin by careful application to the nail plate only as well as reduction of exposure to residual monomers by fast polymerization within a few seconds to minutes. Since this kind of product is not meant to be applied on the skin, but on nails only, there is no risk from systemic exposure, even if insignificant amounts will have contact with the skin. In case of unintended skin contact, the instructions call for its immediate removal from the skin, especially prior to radiation.
After application of HEMA-containing nail products to the nail plate, the polymerisation process starts immediately and is completed within less than 2 minutes. HEMA will be consumed rapidly during the polymerisation process. Explorative screening investigations showed that under worst-case conditions, the extractable monomer portion is at maximum in the order of about 0.49 % (4900 ppm), irrespectively of product, curing time and light source. Only this tiny amount would theoretically be available for penetration through the

nail plate. Considering the anatomical structure and the functional characteristics of the nail (see section 7 in the submission dossier: Nail structure and function), proper application to the nail plate will not result in any bioavailable portion of the residual HEMA fraction.

SCCS comment
The SCCS agrees that the nail plate has a very low permeability and that it is unlikely that sufficient amounts of monomers of HEMA and Di-HEMA-TMHDC that are needed to induce sensitisation will reach the nail-bed. However, the problem of an incorrect application by the consumers who may apply the substance not only on the nail plate but also to the surrounding skin remains as a possibility leading to sensitisation. Contact dermatitis to (meth)acrylates has been observed on fingers, probably due to removal of excess polish by rubbing it off with unprotected fingers. It is as yet unknown whether filing or sanding ('roughening') of the nails before application of the monomers will lead to enhancement of penetration.
Only a summary of the above-mentioned explorative screening investigations on extractable monomers was available (see 3.1.9).

Ref.: Gatica-Ortega et al., 2017

4.3.5 Repeated dose toxicity

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4.3.6 Mutagenicity / Genotoxicity

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4.3.7 Carcinogenicity

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4.3.8 Reproductive toxicity

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4.3.9 Toxicokinetics

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4.3.10 Photo-induced toxicity

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4.3.11 Human data

A. HEMA

Sensitisation data from several patch test studies conducted on patients suspected to be affected by contact dermatitis to acrylates in nail styling products are summarised in Table 3. Not all studies distinguish clearly between consumers and professionally exposed subjects ('nail stylists', beauticians etc).

Table 3: Overview on patch test results from case reports and other clinical studies with HEMA among patients with skin problems due to nail styling.

Patients	No. of positive reactions to HEMA	Exposure/Remark	Reference
1 patient	Positive	Cosmetician	Conde-Salazar 1986
5 patients	5/5 positive to HEMA	5 women with dermatitis from photo-bonded acrylic nails	Hemmer 1996
337 patients out of 440 were patch tested with HEMA	29/337 were positive	440 patients identified with exposure to acrylates and methacrylates out of 14000 records. 67/440 patients showed at least one relevant reaction to acrylate patch tests. 47/67 patients were sensitized at work (3/47 were beauty therapists); of the remaining patients, 16 were sensitised via artificial nails.	Tucker 1999
55 patients	21/55 female patients positive to allergens from the methacrylate artificial nail series (14/22 were professional beauticians). Of the 55 patients, 17 had a positive reaction to HEMA. Of these, 9 were consumers and 8 were professionally exposed	All 55 patients were women professionally and non-professionally exposed to artificial nail products. Study period 2001 to 2004.	Lazarov 2007
122 patients	37/122 patients were positive to (meth)acrylates. HEMA was positive in 30. Of the 37 positive cases, 20 were beauty technicians and 8 were consumers.	Observational and retrospective study (2006-2013). Among 2263 patch-tested patients, 122 underwent testing with an extended meth(acrylate) series	Ramos 2014

241 patients	16 positive to a (meth)acrylate or cyanoacrylate 12/16 positive to HEMA	A retrospective observational study on 241 consecutive patients patch tested with (meth)acrylates or cyanoacrylates between January 2012- February 2015	Muttardi 2014
87 patients	27/87 positive to HEMA	87 female patients worked as nail artists/cosmetologists and suspected nail cosmetics as the cause of dermatitis	Uter 2015
8 patients	6/8 positive	8 patients who had reported severe skin reactions after the use of the UV-curing polish, patch tested at five dermatology departments in Sweden	Dahlin 2016
113 patients	37/113 positive	299 patients out of > 110,000 patients were selected as "nail" patients. 113 were specifically tested on HEMA allergy, of which 37 were sensitised.	Schnuch 2016
475 patients	52 positive to (meth)acrylates (24 occupation related). 29 positive to HEMA, for which acrylate nails were responsible in 22)	Retrospective review. A series of 28 (meth)acrylates was applied to 475 patients	Spencer 2016
455 patients	54 were positive to acrylates. Of these, 44 were positive to HEMA. Of the 54 positives to acrylates, 16 were beauticians and 30 had non-professional exposure to nail acrylates.	A retrospective review of all patients tested with acrylates from 2008 to 2014. Not clear how many (12 or 13) of the beauticians and how many of the non-professionally exposed had a positive reaction to HEMA.	Montgomery 2016

230 patients tested on methacrylates; of these, 220 were patch tested to HEMA	198/220 (90%) positive to HEMA	Retrospectively reviewed files of patients with ACD caused by (meth)acrylates related to nail cosmetic products who were patch tested between 2011-2015 in 13 departments of dermatology in Portugal. Not specified the number of consumer positive. Of the 230 investigated patients, 55 were nail stylists, 56 were consumers, and 119 had mixed exposure.	Raposo 2017
18228 patients	136 positive to nail acrylates, 124 to HEMA	Retrospective study about allergic contact dermatitis from acrylates and methacrylates due to artificial nails diagnosed from 2013-15 in several clinics whose members belong to EECDRG	Goncalo 2017, Goncalo 2018
908 patients	97/908 positive to at least one acrylate (21 cases were nail-related cosmetic reactions)	Out of 4758 patients 908 were patch tested to an acrylates series	Rajan 2017
2353 patients	43 patients were diagnosed with allergic contact dermatitis caused by (meyh)acrylates. 39/43 were positive to HEMA	The files of patients with ACD caused by (meth)acrylates in long-lasting nail polish diagnosed between 2013 and 2016 in four dermatology departments in Spain were reviewed	Gatiga-Ortega 2017
4 patients	3 of these 4 sensitised to HEMA	All 4 had positive patch-tests to other acrylates	Gatica-Ortega 2018

Hemmer et al. (1996) investigated five women with damages of nails and of the skin around nails induced by the application of artificial nails with acrylic glues. They showed pruritic dermatitis around and under the nails for several months. Two out of these patients had dermatitis of the lower lids and cheeks. The symptoms developed 6 months to 3 years after the first applications of artificial nails. Monthly renewal of the nails caused a strong exacerbation of the dermatitis within 24 hours.
In the patch test performed with a standard series and a special battery including HEMA and Di-HEMA-TMHDC and other acrylates and (meta) acrylates, all five patients (5) had a positive patch-test to HEMA.
Two patients were positive to Di-HEMA-TMHDC.

Kanerva et al. (1996) also reported a case of 47-year-old female cosmetician who developed dermatitis on her right thumb that subsequently spread to both hands and face after she started to work with photo-bonded nails and chemically cured nail cosmetics. HEMA and other but not all acrylates resulted in a positive skin reaction (+2). The patient had also a positive allergic patch test result to her own nail strengthener preparation that contained 2.2% Butyl Methacrylate and her own monomer liquid for sculptured nails with 5% Triethylene Glycol Dimethacrylate.

A retrospective study (Tucker 1999) over a 15-year period identified 440 patients (professionally and non-professionally exposed) out of approximately 14,000 records with a history of exposure to acrylates and methacrylates. All 440 had been patch tested with HEMA; in 67 (15.2%) there was a positive reaction. 19 out of the 67 positive patients had been exposed to nail-styling products.

Lazarov (2007) conducted a 4-year retrospective study of patients with suspected ACD from artificial nails (ANs). Patients were tested with the methacrylate artificial nail series and were evaluated clinically and with patch test examination.
About half of the patients were beauticians specialising in nail sculpturing who developed Occupationally-related ACD.
Of the 55 patients reacting to acrylates, 17 had a positive reaction to HEMA. Of these, 9 were consumers and 8 were professionally exposed.

Uter (2015)_conducted a retrospective analysis (2004-2013) of patch test results with (meth)acrylates, along with clinical and demographic data. These were used to subdivide patients according to (i) a potentially exposed occupation and (ii) nail cosmetics as the suspected cause of contact dermatitis and patterns of co-sensitisation. Among the 114 440 patients patch tested, 72 244 were female and were considered further. 87 patients worked as nail artists or cosmetologists. In this group 31% responded with a positive patch test to HEMA. Among the total number of patients, 47.1% reacted to at least one (meth)acrylate, most often to HEMA (n = 27), 2-hydroxypropyl methacrylate and hydroxyethyl acrylate (n = 26 each), with marked coupled reactivity. In other subgroups of interest, frequencies of sensitisation to (meth)acrylates were less elevated but higher than in all remaining female patients (n = 69 419). The authors concluded that the results indicate a fairly uncommon, but potentially serious, problem, especially concerning professionally exposed and sensitised nail artists.

Ramos (2014) performed an observational and retrospective study (January 2006-April 2013) to evaluate and correlate epidemiological and clinical parameters and positive patch test results with (meth)acrylates. Among 2263 patch-tested patients, 122 underwent testing with an extended (meth)acrylate series. Twenty-eight cases were related to artificial nails. In their sample, beauty technicians working with artificial nails were the most affected group (80% of occupational cases including industrial workers and dentists).

Dahlin (2016) reported severe undesirable effects in 8 patients caused by methacrylate ultraviolet-curing nail polish for non-professional use. Out of these, 6 had a positive patch test to HEMA.
The same 8 patients were also patch-tested with Di-HEMA-TMHDC in 2% petrolatum; 7 were positive and one had a doubtful reaction.

Geier (2016) performed a retrospective analysis of patch test results with (meth-) acrylates including clinical and demographic data to analyse the frequency of contact allergy to (meth) acrylates used in artificial nails in nail artists as well as in consumers. Altogether 72,244 female patients were patch tested between 2004 and 2013. Only in 398 out of 72,244 female patients (0.55%), this product category was explicitly mentioned. If nail artists and cosmetologists were added, the patient portion increased to 732 cases (1.01%). The investigators concluded that contact allergy to (meth-)acrylates was much more common among nail artists with suspected allergic contact dermatitis to nail materials (47.1%) than among consumers with suspected allergic contact dermatitis to nail materials (18.0%).
The authors state that their data are the result of clinical epidemiology (and not population-based epidemiology), and have therefore to be put into perspective by a quantitative view.
For general risk considerations, the authors pointed out that patients attending their skin clinic are a highly selected subgroup of the general population, with a selection driven by morbidity. Thus, in absolute terms, the risk in the general population is much lower than 0.55% as in their data, at least by a factor of ten.

Schnuch_(2016) provided results from a dermatological (Dermatological surveillance of the Information Network of Departments of Dermatology (IVDK) on contact allergies with 56 departments participating, and with an annual entry of data from about 12,000 patients based also on data Uter (2015). The analysis on nail cosmetics during a ten year period of total accumulated data comprised 112,327 patients. Out of this collective, 299 patients were selected as "nail" patients on the base of clinical symptoms, 113 of whom were specifically tested for HEMA contact allergy; of these, 37 (33 %) were shown to be sensitised. With regards to the overall patients, the authors considered this as a negligible proportion of 0.03% if compared to the total number of patients tested. They commented on this percentage because only 300 patients were selected as nail patients and 113 were specifically tested for HEMA.

Spencer (2016) applied a series of 28 (meth)acrylates to 475 patients. Results were positive in 52 cases, with occupational sources being identified in 24.
29/52 patients were positive to HEMA. 22 of the 29 positive patients were exposed to acrylates for nails application. These were both consumers and nail professionals.

Montgomery (2016) reported from the UK a retrospective review of all patients tested with acrylates over a 6-year period (200-2014). 4710 patients underwent patch testing and 455 of these were tested with an acrylates series. Of the 455 tested with acrylates, 54 showed positive reactions. Of these, 44 (81.2%) were allergic to HEMA. Seventeen (31.5%) of the 54 were occupationally-related and all but one of these patients were beauticians. Among occupational cases, 13 (92.9%) were allergic to HEMA. Thirty-seven patients had non-occupational allergic contact dermatitis. Of these, 30 (81%) cases were deemed to be related to nail products containing acrylates.

Raposo (2017) published the results of a retrospective review on patients patch tested for acrylate contact dermatitis related to nail cosmetic products, summarising the results from 13 departments of Dermatology in Portugal from 2011 - 2015.
Of 230 cases of ACD, 55 cases were professionally exposed as technicians, 56 were consumers and 119 had mixed exposure from professional and non-professional contact with acrylates. Most of the patients presented with chronic hand eczema (93%).
HEMA was tested in 220 patients, of which 190 tested positive.

In a Spanish study (Gatica-Ortega 2017) on 2353 patients patch tested positive to (meth)acrylates, 43 (1.82%) were diagnosed with allergic contact dermatitis caused by (meth)acrylates in long-lasting nail polish. The most frequent positive allergens were HEMA, 2-hydroxypropyl methacrylate (HPMA), and tetrahydrofurfuryl methacrylate (THFMA). In all patients with allergic contact dermatitis to (meth)acrylates, the fingers were involved, where eczema on the dominant hand usually was more severe. This was probably related to excess polish being removed without the use of appropriate material. The excess material was usually removed by rubbing it off with the unprotected dominant fingertips. Face dermatitis was observed in 15 of 40 (37.5%) patients, and was probably mainly attributable to accidental transfer of excess polish material by contaminated fingers or objects. Most cases were diagnosed in an occupational setting. This study gives evidence that professionals handling the substance without safety measures are likely to expose their skin.

Following a call for data by the European Commission the reports described below were submitted:

On behalf of the European Environmental Contact Dermatitis Research Group (EECDRG), Gonçalo (2017) reported retrospective studies on allergic contact dermatitis (ACD) from acrylates and methacrylates due to artificial nails diagnosed during the years 2013-15 in several clinics.
During the commenting period for this opinion, updated figures were published (Gonçalo 2018). ACD from nail (meth)acrylates was diagnosed in 135 females and one male out of 18228 patients. Exposure to nail (meth)acrylates occurred mostly in an occupational setting (77 cases – 57%, but higher in southern Europe – 84%). Fifty-nine patients were exposed to (meth)acrylates only during the process of sculpting their own artificial nails. Most patients reacted to two or more acrylates, while HEMA was the most common allergen (124/135) found both in occupational and non-occupational cases

In a UK multicentre audit (Rajan 2017), HEMA was the most common acrylate causing positive reactions (positive in 97 of 4758 consecutive unselected patch test patients and 10.5% of 908 selected patients).
Nail-cosmetic related reactions were observed in 21 cases.

During the commenting period on the draft opinion, the SCCS was informed about additional cases of contact dermatitis from nail (meth)acrylates: 4 (3/4 reacting to HEMA) from Spain (Gatica-Ortega 2018) and 16 from the Netherlands (13/16 reacting to HEMA, half of them professionally exposed).

SCCS comment on human studies with HEMA
Several clinical studies have been conducted with the 72-hour patch test method to test acrylate sensitisation in large patient populations. These patients were selected based on a diagnosis of suspected allergic contact dermatitis to acrylates. The patients in these studies were made up of a mixed population comprising patients exposed for professional reasons (dentists, industry workers), those working as professional nail stylists, and consumers exposed to contact with artificial nails that require an adhesive application based on acrylates. Not all of the studies have a clear division between patients that are just consumers and professional nail stylists; often the patients seem to have mixed exposure as both a consumer and professional nail stylist
Compared to the professional users of artificial nail systems, the positive reactions to HEMA seem to be less common among those who are only consumers. Although the number of users is not known, the data should be interpreted in the context of the apparently widespread exposure among consumers and the number of professional users of artificial nail products.

The publications indicate that there is often co-sensitisation to other (meth)acrylates.

B. Di-HEMA-TMHDC

In Table 4 the patch test studies with Di-HEMA-TMHDC, mostly conducted on populations other than users of nail-styling products, are summarised.

Table 4: Overview on patch test results from case reports and other clinical studies regarding Di-HEMA-TMHDC exposed patients (professionally and not professionally exposed)

Subjects	No. of positive reactions	Exposure/Remark	Reference
1 dentist,6 dental nurses	0/5	Assumed acrylate sensitisation towards plastic resins, positive reactions towards other (meth)acrylates	Kanerva 1989
5 patients with photo-bonded acrylic nails and dermatitis	2/5	Patients developed symptoms 6 months to 3 years after first applications; monthly renewal caused strong exacerbation within 24 hours.	Hemmer 1996
1 cosmetician	1/1	A 47-year-old female cosmetician developed dermatitis on her right thumb that subsequently spread to both hands and face after she started to work with photo-bonded nails and chemically cured nail cosmetics	Kanerva 1996
268 patients	2 positive	Patients out of 440 in total from about 14,000 records with a history of acrylates and methacrylates exposure	Tucker 1999
13833 patients	54/13833 showed positive patch test to 1 or more (meth)acrylates (23 were non-occupationally exposed and 31 were occupational) Out of the 54 positive patients , one (1.4%) reacted to Di-	13833 patients suspected of contact dermatitis examined during 1978 – 1999	Geukens 2001

	HEMA		
8 patients	7/8 showed positive reactions and 1/8 showed a doubtful reaction	8 patients who had reported severe skin reactions after the use of the UV-curing nail polish were patch tested at five dermatology departments in Sweden.	Dahlin 2016
6775 patients who were dental technicians	47/6775 (0.7%)	Di-HEMA-TMHDC is contained in tests for dental technicians. Least frequent allergen among (meth)acrylates. Tests between 2008 – 2015.	Geier 2016
10 patients reacting to 'urethane dimethacrylate'		Not clear how many patients had been patch-tested with Di-HEMA-TMHDC	Gonçalo 2018

Kanerva (1989) reported that none of five patients (4 dental nurses and 1 dentist) occupationally sensitised to dental resin products reacted to Di-HEMA-TMHDC 2% in petrolatum when patch tested with the European standard and special acrylates series.

Hemmer (1996) investigated five women with photo-bonded acrylic nails who had pruritic, paronychial and subonychial dermatitis. In the patch tests performed with a standard series and a special battery including acrylates and methacrylates, one patient and two patients reacted positively to 0.2% and 0.6% Di-HEMA-TMHDC.

Kanerva (1996), reported a positive reaction in a 47-year-old female cosmetician who developed dermatitis on her right thumb that subsequently spread to both hands and face after she started to work with photo-bonded nails and chemically cured nail cosmetics. The patient also had a positive patch test to other (meth)acrylates and to her own nail strengthener preparation..

Tucker (1999) reported that, over a 15-year period, in total 440 patients out of approximately 14,000 records with a history of exposure to acrylates and methacrylates were identified. Two out of 268 patients (0.7%) who were patch tested with 2% Di-HEMA-TMHDC showed a positive response.

Geukens (2001) reported that among 13,833 patients suspected of contact dermatitis examined during the years 1978-1999, 54 patients showed a positive patch test to one or more (meth)acrylates (23 subjects were non-occupationally exposed and 31 were occupationally exposed). Out of the 54 positive patients, one (1.4%) reacted to Di-HEMA-TMHDC.

Dahlin (2016) investigated eight patients who had reported severe skin reactions after the use of the UV-curing polish; they were patch tested at five dermatology clinics Sweden. It was shown that all 8 patients showed contact allergic reactions towards Di-HEMA-TMHDC.

Geier (2016) performed a study on dental technicians with occupational dermatitis. Di-HEMA-TMHDC has been patch tested in this series in 6775 patients during the years 2008 to 2015 (total number of patients: 99,130). 47/6775 (0.7%) patients showed a reaction. Thus, it was the least frequent allergen among the (meth-)acrylates in this series. Therefore, the authors concluded that there is no conclusive indication that Di-HEMA-TMHDC represents a special, frequent, or particularly severe allergological problem, compared to other methacrylates.

In the retrospective study of records from 18228 patients in 13 departments participating in the EECDR, there were 10 patients with a positive reaction to 'urethane dimethacrylate' (Gonçalo 2018). It was not clear how many had been patch-tested with Di-HEMA-TMHDC.

SCCS comment on human (patch-test) studies with Di-HEMA-TMHDC

There are only a few reports with information on sensitisation to Di-HEMA-TMHDC among users of nail-styling products. Di-HEMA-TMHDC is commonly used in dentistry and more reports are available from this professional group. The LLNA indicates that it is a weak sensitiser. This is reflected in the clinical studies in humans, especially the study among dental technicians (Geier 2016) which indicates that this was the least frequent allergen among the acrylates. The human studies do not indicate that sensitisation to Di-HEMA-TMHDC is of concern among users of nail-styling products.

Respiratory effects among professional users

Several epidemiological studies among professionals applying and sculpturing artificial nails point towards an increased risk of asthma (Kreiss 2006; Reutman 2009; Roelofs 2008). A clinical study with simulated inhalation exposure to nail-styling work using different acrylates among two professionals with asthmatic complaints established occupational asthma (Sauni 2008). Interestingly, one of these cases had also been diagnosed with allergic contact dermatitis with contact sensitisation to 2-HEMA and to ethylene glycol dimethylacrylate (EGDMA). Three out of 10 nail-stylists with occupational allergic contact dermatitis to acrylates experienced exacerbation of pre-existing asthma (Lazarov 2007). In a study among 71 nail stylists who responded to an invitation for a clinical respiratory examination, rhinitis (in 21%) was detected, as well as an overall tendency to reduced expiratory flow (FEV) and diffusion (Dessalces 2014).

4.3.12 Discussion

Physicochemical properties

Data on the impurities in HEMA and Di-HEMA-TMHDC, in particular the presence of possible sensitisers, have not been provided.
Additional information on the stability studies (conditions, any stabiliser added, analytical method used to evaluate stability) is not provided.
Information on the speed and completeness of the polymerisation and persistence of Di-HEMA-TMHDC monomer under use conditions along with information on the concentration and the type of polymerisation inhibitors and polymerisation activators is not provided.
Information on various commercial systems used for polymerising HEMA and Di-HEMA-TMHDC is also not provided.

Nail penetration

Penetration of the nails by pharmaceuticals (mainly anti-fungal agents) has generally been insufficient to deliver the desired dosage. Several studies show that the nail plate behaves like a hydrophilic-gel barrier and is not lipophilic (Mertin 1997, Brown 2009. Kobayashi 2004, Kobayashi 1999). Nail permeability is however independent of lipophilicity, but clearly decreases with increasing molecular weight (Kobayashi 2004). Flux through the nail plates of caffeine, methylparaben and Terbenafine are in the order of 0.55 to 6.5 microgram per cm2 per hour (Brown 2009). The flux of p-Hydroxybenzoic acid methyl ester - methylparaben - (which has a molecular weight close to that of HEMA) was estimated to be approx. 15 microgram per cm2 per half a day (Kobayashi 2004).
In view of these studies, and considering that polymerisation is initiated immediately after application, it can be assumed that monomers of HEMA and di-HEMA-TMHDC penetrate the nails only in negligible amounts. In view of the moderate sensitisation potency, it can also be assumed that induction of sensitisation is unlikely from the very small amounts that could theoretically be presented to the immune system at the level of the nail bed.

It is as yet unknown whether filing or sanding ('roughening') of the nails before application will lead to nail penetration by methacrylate monomers. A study on components of the nail plate of one human subject indicates that the main nail barrier to drug permeation may be the low diffusivity of drugs in the dorsal (upper) layer of the nail plate (Kobayashi 1999).

Sensitisation

HEMA
The animal studies indicate that HEMA can be considered as an allergen with weak to moderate potency.
The human studies conducted by patch testing among patients in dermatology clinics indicate that this substance can be considered an allergen of concern. However it should be noted that among consumers the sensitisation most likely results from contamination of the skin adjacent to the nails (with a relatively short exposure to a high concentration) or contamination of other skin areas because penetration through the nail plate is likely to be negligible. This means that application that is restricted to the nail plate is safe.
It is as yet unknown whether induction of sensitisation among consumers is driven by unintentional contamination by uncured monomers of the skin adjacent to the nail plates, or by contamination of other skin areas (such as fingertips) by inappropriate handing of the product.
Compared to the consumers (those having their nails treated), the potential for sensitisation to HEMA is considerably higher amongst the professional users when protective measures are neglected. The clinical studies (in patch-tested populations) support this. Besides skin exposure due to inadequate handling of the monomers, the removal of excess nail-polish material using unprotected fingers is also likely to occur.
It should also be noted that the data obtained in clinical studies do not reflect the real incidence in the general population of HEMA contact allergy, which is at the moment unknown. An increase in prevalence may occur due to the increasing popularity of artificial nails. The recent publications seem to point towards an increase.
These publications also indicate that many of the patients reacting to nail acrylates are also sensitised to other (meth)acrylates.

Di-HEMA-TMHDC
There are only a few reports with information on sensitisation to Di-HEMA-TMHDC among users of nail-styling products. Di-HEMA-TMHDC is commonly used in dentistry. The LLNA indicates that it is a weak sensitiser. This is reflected in the clinical studies in humans. The human studies do not indicate that sensitisation to Di-HEMA-TMHDC is of concern among users of nail-styling products.

Respiratory problems have been reported among professional users of nail-styling products, but the causative chemicals are often not identified.

For 'metacrylates' the evidence for respiratory allergy was denoted as limited or contradictory in one review (Baur 2013) and absent in an updated version (Baur 2014).

For professional users, guidelines for the prevention of skin sensitisation and respiratory problems are available (NIOSH 2011). A recent report from the French Authorities (ANSES 2017) reviews and discusses a range of exposures to various chemicals in nail-styling professionals.

5. CONCLUSION

1. In light of the data provided, does the SCCS consider monomers of HEMA and Di-HEMA Trimethylhexyl Dicarbamate, safe at concentrations of up to 35% and 99% respectively when used in topically applied UV-cured artificial nail modelling systems?

The available evidence suggests that normal nail plate acts as a good barrier to penetration of chemical substances in general, and that both methacrylate monomers (HEMA and di-HEMA-TMHDC) polymerise rapidly under UV curing when applied as part of an artificial nail modelling system. This leaves very little chance for the monomers to be absorbed in any appreciable amount through the nail plate. In view of this, the SCCS is of the opinion that HEMA and di-HEMA-TMHDC, when applied appropriately to the nail plate at concentrations of up to 35% and 99% respectively as part of an artificial nail modelling system, are not likely to pose a risk of sensitisation, provided that their use is restricted to the nail plate only and contact with the adjacent skin is avoided.

2. Does the SCCS have any further scientific concerns with regard to the use of HEMA and Di-HEMA Trimethylhexyl Dicarbamate monomers in cosmetic products?

- More analytical data are needed to exclude the possibility of the presence of other sensitisers that may be present as impurities or degradation products alongside the two methacrylate monomers.
- Both HEMA and di-HEMA-TMHDC are weak to moderate sensitisers and pose a risk of sensitisation from misuse of the products or from inappropriately carried out application or from unintentional contamination of the skin adjacent to the nails under normal and reasonably foreseeable conditions of use.
- Filing or sanding nails to remove/replace previous applications may generate particle dust that may lead to respiratory exposure of the professionals if appropriate protective measures are not in place.
- The potential for sensitisation to the methacrylate monomers is likely to be higher amongst the professionals who carry out routine applications of artificial nail modelling systems without appropriate protective measures.
- In view of the growing popularity of artificial nail fashions and the potential use by consumers at home, and considering the observations of several professional dermatological organisations that the prevalence of contact dermatitis from artificial nail products (among which HEMA is an important constituent) is rising, a further increase of the prevalence of sensitisation is possible.

6. MINORITY OPINION

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7. REFERENCES

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