



## OPINION ON the safety of cosmetic ingredients HEMA and Di-HEMA Trimethylhexyl Dicarbamate" - Submission I - (Sensitisation only)

U. Bernauer, L. Bodin, L. Celleno, Q. Chaudhry, P.J. Coenraads, M. Dusinska, J. Ezendam, E. Gaffet, C. L. Galli, B. Granum, et al.

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13 Scientific Committee on Consumer Safety  
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## **OPINION ON**

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

#### **Submission I**

#### **(Sensitisation only)**

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Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

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2 **About the Scientific Committees**

3 Two independent non-food Scientific Committees provide the Commission with the scientific  
4 advice it needs when preparing policy and proposals relating to consumer safety, public  
5 health and the environment. The Committees also draw the Commission's attention to the  
6 new or emerging problems that may pose an actual or potential threat.

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

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

13 **SCCS**

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

19 **Scientific Committee members**

20 Bernauer Ulrike, Bodin Laurent, Celleno Leonardo, Chaudhry Mohammad Qasim, Coenraads  
21 Pieter-Jan, Dusinska Maria, Ezendam Janine, Gaffet Eric, Galli Corrado Lodovico, Granum  
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33 ISSN ISBN

34 Doi ND

35 The opinions of the Scientific Committees present the views of the independent scientists  
36 who are members of the committees. They do not necessarily reflect the views of the  
37 European Commission. The opinions are published by the European Commission in their  
38 original language only.

39 [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/index\\_en.htm](http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm)

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Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

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3 finalisation of this Opinion.

4  
5 **SCCS Members**

6 Dr U. Bernauer  
7 Dr L. Bodin  
8 Dr L. Celleno (Rapporteur)  
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11 Prof. M. Dusinska  
12 Dr J. Ezendam  
13 Dr E. Gaffet  
14 Prof. C. L. Galli  
15 Dr B. Granum  
16 Prof. E. Panteri  
17 Prof. V. Rogiers  
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19 Dr M. Stepnik  
20 Prof. T. Vanhaecke  
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29 All Declarations of Working Group members are available on the following webpage:  
30 [http://ec.europa.eu/health/scientific\\_committees/experts/declarations/sccs\\_en.htm](http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm)

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34 Keywords: SCCS, scientific opinion, cosmetic ingredients, 2-hydroxyethyl methacrylate  
35 HEMA (CAS 868-77-9 and EC 212-782-2), Di-HEMA Trimethylhexyl Dicarbamate (CAS  
36 41137-60-4 / 72869-86-4 and EC 276-957-5), Regulation 1223/2009

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40 Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on the  
41 safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl  
42 Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only),  
43 SCCS/1592/17, 22 December 2017.

Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

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Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

1

2 **1. BACKGROUND**

3

4 The cosmetic ingredients HEMA, with chemical name 2-hydroxyethyl methacrylate (CAS  
5 868-77-9, EC 212-782-2), and Di-HEMA Trimethylhexyl Dicarbamate, with chemical name  
6 7,7,9 (or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl  
7 bismethacrylate (CAS 41137-60-4/72869-86-4, EC -/276-957-5) are active components of  
8 topically applied artificial nail modelling systems cured by ultraviolet (UV) light. The  
9 methacrylate ester monomers HEMA and Di-HEMA Trimethylhexyl Dicarbamate are used as  
10 film forming ingredients in nail products, where they are consumed within a few seconds to  
11 minutes during the polymerization induced by the UV-curing process.

12

13 In August 2014, the Commission was informed of a decision of the Swedish authorities to  
14 withdraw and prohibit the sale and delivery of a range of nail polishes, according to Article  
15 27 (Safeguard clause) of Regulation (EC) No 1223/2009 on cosmetic products. These  
16 products were notified through the RAPEX system, pursuant to Article 12 of Directive  
17 2001/95/EC on general product safety, as posing a serious risk to consumers (RAPEX  
18 notification A12/1226/14).

19

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

26

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

30

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

33

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

41

42 **2. TERMS OF REFERENCE**

43

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

47

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

50

51

52

Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

1 **3. OPINION**

2 **3.1 Chemical and Physical Specifications**

3 **3.1.1 Chemical identity**

4 **3.1.1.1 Primary name and/or INCI name**

5 INCI names: HEMA and Di-HEMA TRIMETHYLHEXYL DICARBAMATE

6 **3.1.1.2 Chemical names**

7 **HEMA**

8 Chemical name: 2-Hydroxyethyl methacrylate

9 IUPAC name: 2-Hydroxyethyl methacrylate

10 **Di-HEMA Trimethylhexyl Dicarbamate**

11 Chemical name: Di-HEMA trimethylhexyl dicarbamate

12 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

13 Ref: CosIng

14 **3.1.1.3 Trade names and abbreviations**

15 **HEMA**

16 2-HEMA

17 2-Hydroxyethyl ester, methacrylic acid

18 Ethylene glycol methacrylate

19 HEMA

20 Hydroxyethyl methacrylate

21 **Di-HEMA Trimethylhexyl Dicarbamate**

22 Depositor-Supplied Synonyms:

23 Urethane dimethacrylate

24 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

25 7,7,9(or 7,9,9)-trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diyl bismethacrylate

26 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

27 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

28 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

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Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

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

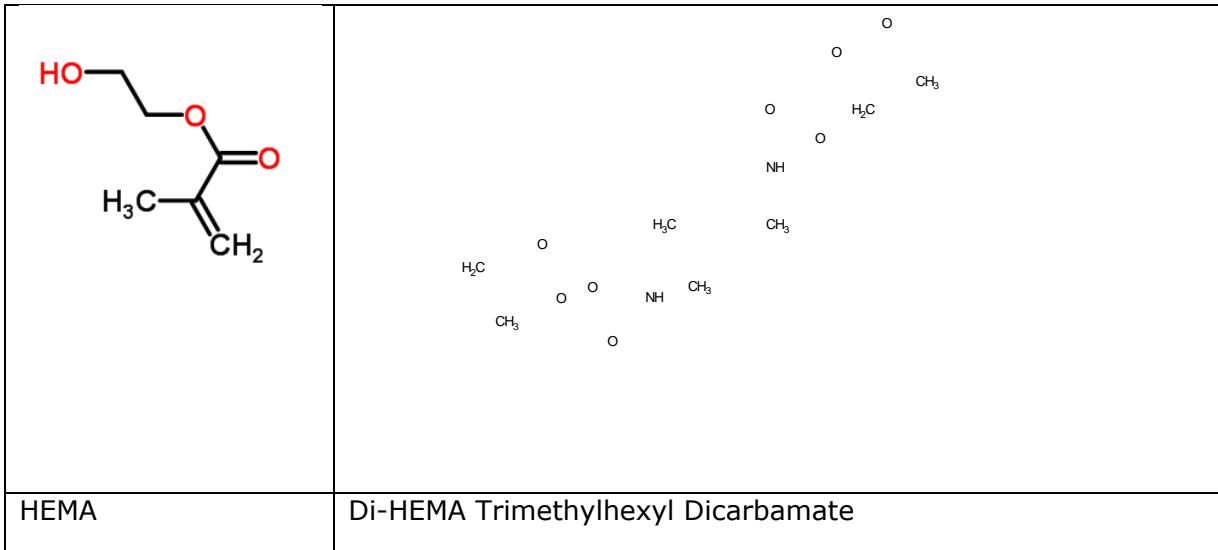
10  
11  
12 Ref: PubChem: <https://pubchem.ncbi.nlm.nih.gov/compound/170472#section=Synonyms>,  
13 CIR, 2005; OECD SIDS, 2001  
14  
15

16 3.1.1.4 CAS / EC number

17  
18 HEMA:  
19 CAS: 868-77-9  
20 EC: 212-782-2

21  
22 Di-HEMA Trimethylhexyl Dicarbamate:  
23 CAS: 41137-60-4, 72869-86-4  
24 EC: 276-957-5

25 3.1.1.5 Structural formula



28  
29 Ref: ChemSpider, PubChem  
30  
31

32 3.1.1.6 Empirical formula

33  
34 Formula HEMA: C<sub>6</sub>H<sub>10</sub>O<sub>3</sub>  
35 Formula Di-HEMA: C<sub>23</sub>H<sub>38</sub>N<sub>2</sub>O<sub>8</sub>

Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

1                   **3.1.2 Physical form**

2                   Physical form HEMA: Clear liquid

6                   **3.1.3 Molecular weight**

8                   Molecular weight HEMA: 130.14 g/mol

9                   Molecular weight Di-HEMA: 470.56 g/mol

12                   **3.1.4 Purity, composition and substance codes**

14                   HEMA:

15                   Purity: 97.0 - >99%

18                   **SCCS comment**

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

23                   **3.1.5 Impurities / accompanying contaminants**

25                   HEMA:

26                   Diethylene glycol mono-methacrylate: < 2.0%

27                   Ethylene glycol di-methacrylate: < 0.2%

28                   Water: < 0.04%

29                   Methacrylic acid: < 0.04%

30                   Ethylene oxide: < 0.001%

31                   4-Methoxy phenol (syn. Hydroquinone Methylether (MeHQ)): 40 – 80 ppm (additive for  
32                   prevention of polymer formation). Noteworthy to mention that in commercial nail products  
33                   for professional and for non-professional use, the MeHQ content will be at maximum 200  
34                   ppm and thus in line with the current cosmetics regulation.

36                   **SCCS comments**

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

42                   **3.1.6 Solubility**

44                   HEMA:

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

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

50                   Di-HEMA Trimethylhexyl Dicarbamate:

51                   Soluble in water: 30 mg/L at 37 °C (experimental, ChemIdPlus)

53                   Reference: OECD SIDS, 2001; Keystone, 2016

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1

2

### 3.1.7 Partition coefficient (Log Pow)

4

5 HEMA:

6 Log Pow: measured: 0.42 at 25 °C and pH ≥ 5.9 – ≤ 6.1 (OECD  
7 107)

8

9 DI-HEMA Trimethylhexyl Dicarbamate:

10 LogPow = 4.69 (estimated, ChemIdPlus)

11

12

### 13 3.1.8 Additional physical and chemical specifications

14

15

16 **HEMA**

17 Melting point: -12 °C (experimental, Alfa Aesar, ChemSpider)

18

Boiling point: 250 °C (experimental, Alfa Aesar, ChemSpider)

19

Flash point: 101 °C (experimental, Alfa Aesar, ChemSpider)

20

Density: 1.1±0.1 g/cm<sup>3</sup> (predicted, ACD/Labs, ChemSpider)

21

Vapour pressure: 0.2±0.7 mmHg at 25°C (predicted, ACD/Labs, ChemSpider)

22

Viscosity: /

23

pKa: /

24

Refractive index: 1.453 (experimental, Alfa Aesar, ChemSpider)

25

UV\_Vis spectrum: /

26

27

28 **Di-HEMA Trimethylhexyl Dicarbamate (Di-HEMA-TMHDC):**

29

Melting point: /

30

Boiling point: 594.3±45.0 °C at 760 mmHg (predicted, ACD/Labs, ChemSpider)

31

Flash point: 313.2±28.7 °C (predicted, ACD/Labs, ChemSpider)

32

Vapour pressure: 0.0±1.7 mmHg at 25°C (predicted, ACD/Labs, ChemSpider)

33

Density: 1.1±0.1 g/cm<sup>3</sup> (predicted, ACD/Labs, ChemSpider)

34

Viscosity: /

35

Surface Tension: 37.6±3.0 dyne/cm (predicted, ACD/Labs, ChemSpider)

36

pKa: /

37

Refractive index: 1.479 (predicted, ACD/Labs, ChemSpider)

38

Molar Refractivity: 122.0±0.3 cm<sup>3</sup> (predicted, ACD/Labs, ChemSpider)

39

UV\_Vis spectrum: /

40

41

Ref: [www.chemspider.com](http://www.chemspider.com)

42

43

### 44 3.1.9 Homogeneity and Stability

45

46

47 **HEMA:**

48

The product is stable

49

50

Ref: Keystone, 2016

51

52

**SCCS comment**

53

54

55

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.

## Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

1  
2  
3 **Polymerisation**

4 The polymerization of 22 methacrylates including HEMA was measured in an ethyl  
5 methacrylate based system using Differential Scanning Calorimetry (DSC). Maximum peak  
6 exotherm and total exotherm were measured as indications for the polymerization process,  
7 while the nail enhancement product reacted in the test chamber. Maximum peak exotherm  
8 occurs at gelation (gel point) of a curing nail enhancement system. The gelation point is  
9 reached when at least 50% of the monomer has reacted and the material has a hardened  
10 surface. This process starts immediately and takes 2 to 4 minutes in most commercially  
11 available professional monomer-based nail enhancement systems. Changes in gel point  
12 time and total exotherm are both directly proportional to the test monomers' reactivity.  
13 In the experiment, the Radical® artificial nail monomer/polymer system was modified by  
14 adding 5% ethyl methacrylate to establish a normalised baseline to compare reactivity of  
15 various test monomers including HEMA. Each of the 22 test monomers were added at a  
16 concentration of 5% and 50% (by weight) to the Radical® artificial nail monomer/polymer  
17 system.

18 The results show that polymerization of HEMA was fast in general and even faster at a  
19 higher concentration (Table 1). This can be considered as an indication of strong reactivity.  
20  
21

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

| HEMA concentration  | 5%  | 50%                            |
|---------------------|-----|--------------------------------|
| Polymerization time | set | 2.85 ± 5.0 min                 |
| Total exotherm      |     | 672.07 ± 4.4 mJ/m <sup>2</sup> |
|                     |     | 1130.3 ± 6.3 mJ/m <sup>2</sup> |

22  
23 Ref: Creative Nail Design, 2001; Schoon, 1994a + b  
24  
25  
26

**Extraction**

27 Explorative analytical screening investigations to mimic use conditions are available. The  
28 amount of extractable Hydroxyethyl Methacrylate (HEMA) amongst other methacrylates  
29 from cured films of UV/LED full coat system, an acrylic and a builder system, applied on a  
30 glass slide, was analysed using a 0.1% salt water solution or acetone as extraction solvent.  
31 The salt water extracts were analysed by High Performance Liquid Chromatography (HPLC)  
32 and the acetone extracts were analysed by Gas Chromatography (GC).  
33 The HEMA containing samples were prepared as follows:

## 34 Preparation of Samples

35 NC6195M: Base coat was applied to a glass slide using a 5 mil drawdown bar and cured for  
36 3 minutes in Young Nails UV lamp. The first colour coat was applied to the glass slide using  
37 a 10 mil drawdown bar and cured for 3 minutes. The second colour coat was applied to the  
38 glass slide using a 15 mil drawdown bar and cured for 3 minutes. The top coat was applied  
39 using a 20 mil drawdown bar and then cured for 3 minutes. The surface was then wiped  
40 with isopropyl alcohol. The slide was left to sit at room temperature for 72 hours.

41 NC6195N: Base coat was applied to a glass slide using a 5 mil drawdown bar and cured for  
42 1 minute in OPI Studio LED lamp. The first colour coat was applied to the glass slide using a  
43 10 mil drawdown bar and cured for 1 minute. The second colour coat was applied to the  
44 glass slide using a 15 mil drawdown bar and cured for 1 minute. The top coat was applied  
45 using a 20 mil drawdown bar and then cured for 1 minute. The surface was then wiped with  
46 isopropyl alcohol. The slide was left to sit at room temperature for 72 hours.

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1 NC61950-1 & -2: A nail brush was dipped in J2 monomer to wet it. The brush was then  
2 dipped into P3 acrylic powder. The wet powder was then applied to a glass slide and left to  
3 sit at room temperature for 72 hours. Thereafter, the cured film was scraped off the glass  
4 slide and transferred to a glass vial. The weight of the cured film was recorded. The salt  
5 water solution was added to one of the duplicate samples and acetone was added to the  
6 other. The samples were allowed to extract at room temperature for approximately 24  
7 hours. Then, the salt water solution extracts were analysed on an Agilent 1290 HPLC with a  
8 diode array detector and the acetone extracts were analysed on an Agilent 6890 GC with an  
9 FID detector.

10 All HPLC and GC system suitability requirements were met. The detector response to  
11 concentration was linear for the range tested in all standards. The limit of detection (LOD)  
12 was 1.0 ppm for both the HPLC and GC analysis.

15 **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

17  
18 There was no significant difference between the curing time, the light source, the applied  
19 product or the extraction medium, when normal analytical variation was considered. Curing  
20 for 1 min using LED light resulted in a comparable extractable amount of HEMA compared to  
21 3 min curing under UV light. Even following a hardening process without artificial light  
22 exposure led to a comparable amount of extractable HEMA.

23  
24 In any case the extractable HEMA portions were in the same order of magnitude and ranged  
25 between 0.28 % – 0.49 % using salt water and between 0.3 % – 0.49 % with acetone as  
26 extraction medium (Reference: Steffier, 2016).

27  
28 However, these explorative analytical screening data represent a worst case situation and  
29 should therefore not be used for general regulatory purposes, e.g., not to fix specific limit  
values.

32 **SCCS comment**

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

38 **3.2 Function and uses**39 From the submission:

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

Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

1 component powder/liquid systems (self- or light curing) and light-curing single component  
2 gel systems (composites). The current and anticipated use concentrations of HEMA are up  
3 to 10% in powder/liquid systems and up to 35% in gel systems. The artificial nail modelling  
4 systems are used for fingernails- and toenails.

5 HEMA will be consumed rapidly during the polymerisation process (within 1.82 minutes).  
6 Explorative screening investigations showed that under worst-case conditions, the  
7 extractable monomer portion is at maximum in the order of about 0.49 % (4900 ppm).  
8 For both nail modelling systems, quantities of 2 to 4 g are used for the first application and  
9 approximately 1 g for filling up after approximately 2 to 3 weeks, corresponding to a  
10 maximum of 1400 mg HEMA in total for all nail plates. Contact is meant to be limited to the  
11 keratin of the nail plate.

12 Clear use instructions and adequate training of professional users should ensure that these  
13 nail products are properly applied, i.e. exclusively to the nail plate and not to the  
14 surrounding skin by ensuring a small space between the cuticle and the nail. Thus, there is  
15 no contact to skin when carefully applied to the nail plate. In case of unintended skin  
16 contact at the cuticle and the side of the nails, the use instructions call for removing it  
17 immediately from the skin, especially prior to radiation.

18 For the two-component systems the curing reaction is triggered by mixing the liquid and the  
19 powder. Since the reaction starts immediately and is completed after a maximum of 2 to 3  
20 minutes, processing possibilities are limited in time. The reaction occurs with heating and  
21 odour development.

22 For the light-curing gel systems, which represent a further development of the composites  
23 from dental medicine, curing is started after the decomposition of the added photo  
24 initiators, and the actual curing process is already completed after 30 to 45 seconds. In  
25 practice there is, however, a curing period of 2 to 3 minutes in order to ensure optimum  
26 strength and adhesion of the nail.

27 For the application of the systems there are detailed descriptions, which are selectively  
28 intended to ensure not only optimum application of the nail modelling but also the highest  
29 possible protection of the users.

30 The application of the liquid/powder systems is carried out by means of a special brush,  
31 frequently using a template. With the tip of the brush previously immersed in the liquid, the  
32 powder is absorbed in a slight circulating movement. This forms a wax-like bead. These and  
33 possibly other beads are placed in the centre of the nail and modelled into a slight so-called  
34 C curve. The material thickness is selected in such a way that the entire nail modelling has  
35 at the so-called stress point a maximum height of 1 mm. For the gel systems the principle is  
36 similar, whereby curing by UV light is carried out between the different work steps (gel  
37 applications).

38 Filing is then used to optimise the form, polish and in most cases an additional top coat is  
39 applied to bring about optimum gloss. If necessary, a filling up of the acrylic modelling is  
40 carried out after a few weeks.

41  
42 Ref: Creative Nail Design, 2001; Schoon, 1994a+b, Creative Nail Design, 2013, IKW, 2016  
43  
44

45 **3.3 Toxicological evaluation**

46  
47 **3.3.1 Acute toxicity**

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50 **3.3.2 Irritation and corrosivity**

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Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

1                   **3.3.3 Skin sensitisation**

2                   *Guinea pig maximisation tests (GMPT)*

3                   A GMPT (Clemmensen 1985) investigated the influence of concentration, vehicle, and  
4                   cyclophosphamide on the skin sensitising potential of HEMA. The vehicles used for  
5                   elicitation were petrolatum, soybean oil, and a mixture of soybean oil and 2-butanone  
6                   (sbomek). Ten to twenty guinea pigs (Scg:AL) were used per dose group. The following  
7                   materials were used for intradermal induction (day 0): 1% HEMA (in soybean oil), 25%  
8                   HEMA (in soybean oil), 25% HEMA (in sbomek), 1% HEMA (aqueous), 10% HEMA  
9                   (aqueous), and 25% HEMA (aqueous). Dermal induction was performed on days 7 and  
10                   8 using a 10% sodium lauryl sulfate pre-treatment and 400 µl of HEMA applied via a 48  
11                   h patch. Challenge was performed on day 21 using 25% HEMA (in petrolatum), 25%  
12                   HEMA (aqueous), 25% HEMA (sbomek), 25% HEMA (in soybean oil), and 100% HEMA.  
13                   Effects were scored at 48 h and 72 h post-challenge.

14                   The major determining factor for sensitisation was the concentration used for intradermal  
15                   induction. Induction with 10% HEMA or greater caused a reaction in 4 to 10 guinea pigs  
16                   out of 12 challenged per dose group.

17                   There was no challenge response to challenge when an intradermal injection had been  
18                   given with 1% HEMA in soybean oil. When HEMA was used at concentrations of 25 % or  
19                   higher, the vehicles did not influence the response.

20                   Other guinea pig studies showed (Katsuno 1995, Katsuno 1996) that HEMA produced  
21                   positive delayed hypersensitivity reactions: 6 out of 10 albino guinea pigs induced and  
22                   challenged with HEMA (100%) showed a positive reaction at 24 hours and 5 out of 10  
23                   showed a positive reaction at 48 hours.

24                   The optimum concentration of HEMA for sensitisation and elicitation was established by  
25                   testing HEMA at 0.01, 0.02, 0.1, 0.2, 0.5, 1.0, and 5.0%. Challenge concentrations were  
26                   10, 25, 50, and 100%.

27                   It was shown that the optimum concentration to induce sensitisation was 0.2%; five of five  
28                   guinea pigs had a positive challenge reaction to HEMA at 24 hours and 48 hours after patch  
29                   removal with a mean skin response of 5.0 (Katsuno, 1996).

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

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

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

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

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

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1 Batch: 81106228 (purity: 96.99%)  
2 Vehicle: Dimethylformamide (DMF)  
3 Concentrations: 0, 10, 25, 50%  
4 Positive control: hexyl cinnamic aldehyde  
5 Route: Epidermal (topical) application on the surface of the dorsal ear lobe  
6 GLP: Yes  
7 Published: No  
8 Remark: The study is currently in a negotiation process.  
9

10 The sensitising potential of Di-HEMA-TMHDC was tested at concentrations of 10, 25 and  
11 50% (w/w) solution in DMF (dimethylformamide). The 50% concentration was the highest  
12 non-irritant test concentration which did not show any signs of irritation or systemic toxicity  
13 up to day 8 after three-day exposure to two animals. The application volume 25 µL was  
14 spread over the dorsal surface of the ear lobes once daily for three consecutive days. Five  
15 days after the first application, all mice were intravenously injected with 250 µL of [<sup>3</sup>H]-  
16 thymidine.

17 *Results*

18 Stimulation Indices (SIs) of 1.58, 1.70 and 4.44 were determined at concentrations of 10,  
19 25, and 50% (w/w) in DMF, respectively. A clear dose response was observed. Based on the  
20 SI values, an EC3 value of 36.9% was calculated. A statistically significant increase in the  
21 DPM values was observed in all dose groups in comparison to the vehicle control group.  
22 Based on the calculated EC3 value, Di-HEMA-TMTDC was, under the condition of this LLNA,  
23 considered as a weak sensitisier.

24 Ref: information taken from the submission

25 **SCCS comment on the animal studies**

26 Studies in guinea pigs:

27 While for most studies it is unclear whether the OECD guidelines were followed, induction of  
28 sensitisation was achieved in a number of tests with injection of Freund's adjuvant.  
29 Although guinea pig tests are not suitable to establish potency, the available data point  
30 toward HEMA being a moderate skin sensitisier.

31 *LLNA*

32 HEMA was not tested in the LLNA. Therefore, no information on the skin sensitising potency  
33 is available.

34 The LLNA with Di-HEMA-TMHDC indicates that it is a weak sensitisier.

35 **3.3.4 Dermal / percutaneous absorption**

36 From the submission dossier

37 There is no dermal penetration study available for HEMA.  
38 However, exposure to HEMA is negligible when adhering to proper use conditions, i.e. no  
39 contact to skin by careful application to the nail plate only as well as reduction of exposure  
40 to residual monomers by fast polymerization within a few seconds to minutes. Since this  
41 kind of product is not meant to be applied on the skin, but on nails only, there is no risk  
42 from systemic exposure, even if insignificant amounts will have contact with the skin. In  
43 case of unintended skin contact, the instructions call for its immediate removal from the  
44 skin, especially prior to radiation.

45 After application of HEMA-containing nail products to the nail plate, the polymerisation  
46 process starts immediately and is completed within less than 2 minutes. HEMA will be  
47 consumed rapidly during the polymerisation process. Explorative screening investigations  
48 showed that under worst-case conditions, the extractable monomer portion is at maximum  
49 in the order of about 0.49 % (4900 ppm), irrespectively of product, curing time and light  
50 source. Only this tiny amount would theoretically be available for penetration through the  
51 skin.

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

5 **SCCS comment**

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

15 Only a summary of the above-mentioned explorative screening investigations on extractable  
16 monomers was available (see 3.1.9).

17 Ref.: Gatica-Ortega et al., 2017  
18  
19  
20

21 **3.3.5 Repeated dose toxicity**

22 /  
23  
24

25 **3.3.6 Mutagenicity / Genotoxicity**

26 /  
27  
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29 **3.3.7 Carcinogenicity**

30 /  
31  
32

33 **3.3.8 Reproductive toxicity**

34 /  
35  
36

37 **3.3.9 Toxicokinetics**

38 /  
39  
40

41 **3.3.10 Photo-induced toxicity**

42 /  
43  
44

45 **3.3.11 Human data**

46  
47 **A. HEMA**

48  
49  
50 Sensitisation data from several patch test studies conducted on patients suspected to be  
51 affected by contact dermatitis to acrylates in nail styling products are summarised in Table  
52 3. Not all studies distinguish clearly between consumers and professionally exposed subjects  
53 ('nail stylists', beauticians etc).

## Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

1  
2 **Table 3: Overview on patch test results from case reports and other clinical**  
3 **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.<br>67/440 patients showed at least one relevant reaction to acrylate patch tests.<br>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).<br><br>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.<br>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         |

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|              |  |  |                 |
|--------------|--|--|-----------------|
| 241 patients | 16 positive to a (meth)acrylate or cyanoacrylate<br>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 |

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|   |  |  |                    |
|---|--|--|--------------------|
| 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        |
| 15086 patients  | 94 positive to methacrylate, 89 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       |
| 908 patients  | 97/908 positive to at least one acrylate<br>(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 (mehy)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 |

1  
2  
3 Hemmer et al. (1996) investigated five women with damages of nails and of the skin around  
4 nails induced by the application of artificial nails with acrylic glues. They showed pruritic  
5 dermatitis around and under the nails for several months. Two out of these patients had  
6 dermatitis of the lower lids and cheeks. The symptoms developed 6 months to 3 years after  
7 the first applications of artificial nails. Monthly renewal of the nails caused a strong  
8 exacerbation of the dermatitis within 24 hours.

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1 In the patch test performed with a standard series and a special battery including HEMA and  
2 Di-HEMA-TMHDC and other acrylates and (meta) acrylates, all five patients (5) had a  
3 positive patch-test to HEMA.  
4 Two patients were positive to Di-HEMA-TMHDC.  
5  
6 Kanerva et al. (1996) also reported a case of 47-year-old female cosmetician who  
7 developed dermatitis on her right thumb that subsequently spread to both hands and face  
8 after she started to work with photo-bonded nails and chemically cured nail cosmetics.  
9 HEMA and other but not all acrylates resulted in a positive skin reaction (+2). The patient  
10 had also a positive allergic patch test result to her own nail strengthener preparation that  
11 contained 2.2% Butyl Methacrylate and her own monomer liquid for sculptured nails with  
12 5% Triethylene Glycol Dimethacrylate.  
13  
14 A retrospective study (Tucker 1999) over a 15-year period identified 440 patients  
15 (professionally and non-professionally exposed) out of approximately 14,000 records with a  
16 history of exposure to acrylates and methacrylates. All 440 had been patch tested with  
17 HEMA; in 67 (15.2%) there was a positive reaction. 19 out of the 67 positive patients had  
18 been exposed to nail-styling products.  
19  
20 Lazarov (2007) conducted a 4-year retrospective study of patients with suspected ACD from  
21 artificial nails (ANs). Patients were tested with the methacrylate artificial nail series and  
22 were evaluated clinically and with patch test examination.  
23 About half of the patients were beauticians specialising in nail sculpturing who developed  
24 Occupationally-related ACD.  
25 Of the 55 patients reacting to acrylates, 17 had a positive reaction to HEMA. Of these, 9  
26 were consumers and 8 were professionally exposed.  
27  
28 Uter (2015)\_conducted a retrospective analysis (2004-2013) of patch test results with  
29 (meth)acrylates, along with clinical and demographic data. These were used to subdivide  
30 patients according to (i) a potentially exposed occupation and (ii) nail cosmetics as the  
31 suspected cause of contact dermatitis and patterns of co-sensitisation. Among the 114 440  
32 patients patch tested, 72 244 were female and were considered further. 87 patients worked  
33 as nail artists or cosmetologists. In this group 31% responded with a positive patch test to  
34 HEMA. Among the total number of patients, 47.1% reacted to at least one (meth)acrylate,  
35 most often to HEMA (n = 27), 2-hydroxypropyl methacrylate and hydroxyethyl acrylate (n  
36 = 26 each), with marked coupled reactivity. In other subgroups of interest, frequencies of  
37 sensitisation to (meth)acrylates were less elevated but higher than in all remaining female  
38 patients (n = 69 419). The authors concluded that the results indicate a fairly uncommon,  
39 but potentially serious, problem, especially concerning professionally exposed and sensitised  
40 nail artists.  
41  
42 Ramos (2014) performed an observational and retrospective study (January 2006-April  
43 2013) to evaluate and correlate epidemiological and clinical parameters and positive patch  
44 test results with (meth)acrylates. Among 2263 patch-tested patients, 122 underwent  
45 testing with an extended (meth)acrylate series. Twenty-eight cases were related to artificial  
46 nails. In their sample, beauty technicians working with artificial nails were the most affected  
47 group (80% of occupational cases including industrial workers and dentists).  
48  
49 Dahlin (2016) reported severe undesirable effects in 8 patients caused by methacrylate  
50 ultraviolet-curing nail polish for non-professional use. Out of these, 6 had a positive patch  
51 test to HEMA.  
52 The same 8 patients were also patch-tested with Di-HEMA-TMHDC in 2% petrolatum; 7  
53 were positive and one had a doubtful reaction.  
54  
55 Geier (2016) performed a retrospective analysis of patch test results with (meth-) acrylates  
56 including clinical and demographic data to analyse the frequency of contact allergy to

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1 (meth) acrylates used in artificial nails in nail artists as well as in consumers. Altogether  
2 72,244 female patients were patch tested between 2004 and 2013. Only in 398 out of  
3 72,244 female patients (0.55%), this product category was explicitly mentioned. If nail  
4 artists and cosmetologists were added, the patient portion increased to 732 cases (1.01%).  
5 The investigators concluded that contact allergy to (meth-)acrylates was much more  
6 common among nail artists with suspected allergic contact dermatitis to nail materials  
7 (47.1%) than among consumers with suspected allergic contact dermatitis to nail materials  
8 (18.0%).  
9 The authors state that their data are the result of clinical epidemiology (and not population-  
10 based epidemiology), and have therefore to be put into perspective by a quantitative view.  
11 For general risk considerations, the authors pointed out that patients attending their skin  
12 clinic are a highly selected subgroup of the general population, with a selection driven by  
13 morbidity. Thus, in absolute terms, the risk in the general population is much lower than  
14 0.55% as in their data, at least by a factor of ten.  
15 Schnuch\_(2016) provided results from a dermatological (Dermatological surveillance of the  
16 Information Network of Departments of Dermatology (IVDK) on contact allergies with 56  
17 departments participating, and with an annual entry of data from about 12,000 patients  
18 based also on data Uter (2015). The analysis on nail cosmetics during a ten year period of  
19 total accumulated data comprised 112,327 patients. Out of this collective, 299 patients  
20 were selected as "nail" patients on the base of clinical symptoms, 113 of which were  
21 specifically tested for HEMA allergy and 37 were shown to be sensitised. With regards to the  
22 overall patients, the authors considered this as a negligible proportion of 0.03% if compared  
23 to the total number of patients tested. They commented on this percentage because only  
24 300 patients were selected as nail patients and 113 were specifically tested for HEMA. Thus  
25 37 positive patients out of 113 tested for HEMA indicate a positive percentage of 32.7%.  
26  
27 Spencer (2016) applied a series of 28 (meth)acrylates to 475 patients. Results were positive  
28 in 52 cases, with occupational sources being identified in 24.  
29 29/52 patients were positive to HEMA. 22 of the 29 positive patients were exposed to  
30 acrylates for nails application. These were both consumers and nail professionals.  
31  
32 Montgomery (2016) reported from the UK a retrospective review of all patients tested with  
33 acrylates over a 6-year period (2000-2014). 4710 patients underwent patch testing and 455  
34 of these were tested with an acrylates series. Of the 455 tested with acrylates, 54 showed  
35 positive reactions. Of these, 44 (81.2%) were allergic to HEMA. Seventeen (31.5%) of the  
36 54 were occupationally-related and all but one of these patients were beauticians. Among  
37 occupational cases, 13 (92.9%) were allergic to HEMA. Thirty-seven patients had non-  
38 occupational allergic contact dermatitis. Of these, 30 (81%) cases were deemed to be  
39 related to nail products containing acrylates.  
40  
41 Recently, Raposo (2017) published the results of a retrospective review on patients patch  
42 tested for acrylate contact dermatitis related to nail cosmetic products, summarising the  
43 results from 13 departments of Dermatology in Portugal from 2011 - 2015.  
44 Of 230 cases of ACD, 55 cases were professionally exposed as technicians, 56 were  
45 consumers and 119 had mixed exposure from professional and non-professional contact  
46 with acrylates. Most of the patients presented with chronic hand eczema (93%).  
47 HEMA was tested in 220 patients, of which 190 tested positive.  
48  
49 In a Spanish study (Gatica-Ortega 2017) on 2353 patients patch tested positive to  
50 (meth)acrylates, 43 (1.82%) were diagnosed with allergic contact dermatitis caused by  
51 (meth)acrylates in long-lasting nail polish. The most frequent positive allergens were HEMA,  
52 2-hydroxypropyl methacrylate (HPMA), and tetrahydrofurfuryl methacrylate (THFMA). In all  
53 patients with allergic contact dermatitis to (meth)acrylates, the fingers were involved,  
54 where eczema on the dominant hand usually was more severe. This was probably related to  
55 excess polish being removed without the use of appropriate material. The excess material  
56 was usually removed by rubbing it off with the unprotected dominant fingertips. Face

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1 dermatitis was observed in 15 of 40 (37.5%) patients, and was probably mainly attributable  
2 to accidental transfer of excess polish material by contaminated fingers or objects. Most  
3 cases were diagnosed in an occupational setting. This study gives evidence that  
4 professionals handling the substance without safety measures are likely to expose their  
5 skin.

6

7

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

10

11 On behalf of the European Environmental Contact Dermatitis Research Group (EECDRG),  
12 Gonçalo (2017) reported retrospective studies on allergic contact dermatitis (ACD) from  
13 acrylates and methacrylates due to artificial nails diagnosed during the years 2013-15 in  
14 several clinics. ACD from nail (meth)acrylates was diagnosed in 94 female patients out of  
15 15,086 patients. Exposure to nail (meth)acrylates occurred mostly in an occupational  
16 setting (57 cases – 60.6%). Thirty-seven patients were exposed to (meth)acrylates only  
17 during the process of sculpting their own artificial nails. HEMA was the most common  
18 allergen (89/93) found both in occupational and non-occupational cases

19

20 In a UK multicentre audit (Rajan 2017), HEMA was the most common acrylate causing  
21 positive reactions (positive in 97 of 4758 consecutive unselected patch test patients and  
22 10.5% of 908 selected patients).

23 Nail-cosmetic related reactions were observed in 21 cases.

24

25

26 **SCCS comment on human studies with HEMA**

27 Several clinical studies have been conducted with the 72-hour patch test method to test  
28 acrylate sensitisation in large patient populations. These patients were selected based on a  
29 diagnosis of suspected allergic contact dermatitis to acrylates. The patients in these studies  
30 were made up of a mixed population comprising patients exposed for professional reasons  
31 (dentists, industry workers), those working as professional nail stylists, and consumers  
32 exposed to contact with artificial nails that require an adhesive application based on  
33 acrylates. Not all of the studies have a clear division between patients that are just  
34 consumers and professional nail stylists; often the patients seem to have mixed exposure as  
35 both a consumer and professional nail stylist

36 Compared to the professional users of artificial nail systems, the positive reactions to HEMA  
37 seem to be less common among those who are only consumers. Although the number of  
38 users is not known, the data should be interpreted in the context of the apparently  
39 widespread exposure among consumers and the number of professional users of artificial  
40 nail products.

41

42

43 B. Di-HEMA-TMHDC

44

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

47

48

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

| Subjects                   | No. of positive reactions | Exposure/Remark                        | Reference    |
|----------------------------|---------------------------|--|--------------|
| 1 dentist, 6 dental nurses | 0/5                       | Assumed sensitisation towards acrylate | Kanerva 1989 |

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|   |   |  |              |
|---|---|--|--------------|
|   |   | plastic resins, positive reactions towards other (meth)acrylates   |              |
| 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-HEMA | 13833 patients suspected of contact dermatitis examined during 1978 – 1999   | Geukens 2001 |
| 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   | Geier 2016   |

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|  |  |                      |  |
|--|--|----------------------|--|
|  |  | between 2008 – 2015. |  |
|--|--|----------------------|--|

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

5 Hemmer (1996) investigated five women with photo-bonded acrylic nails who had pruritic,  
6 paronychial and subonychial dermatitis. In the patch tests performed with a standard series  
7 and a special battery including acrylates and methacrylates, one patient and two patients  
8 reacted positively to 0.2% and 0.6% Di-HEMA-TMHDC.  
9

10 Kanerva (1996), reported a positive reaction in a 47-year-old female cosmetician who  
11 developed dermatitis on her right thumb that subsequently spread to both hands and face  
12 after she started to work with photo-bonded nails and chemically cured nail cosmetics. The  
13 patient also had a positive patch test to other (meth)acrylates and to her own nail  
14 strengthener preparation..  
15

16 Tucker (1999) reported that, over a 15-year period, in total 440 patients out of  
17 approximately 14,000 records with a history of exposure to acrylates and methacrylates  
18 were identified. Two out of 268 patients (0.7%) who were patch tested with 2% Di-HEMA-  
19 TMHDC showed a positive response.  
20

21 Geukens (2001) reported that among 13,833 patients suspected of contact dermatitis  
22 examined during the years 1978-1999, 54 patients showed a positive patch test to one or  
23 more (meth)acrylates (23 subjects were non-occupationally exposed and 31 were  
24 occupationally exposed). Out of the 54 positive patients, one (1.4%) reacted to Di-HEMA-  
25 TMHDC.  
26

27 Dahlin (2016) investigated eight patients who had reported severe skin reactions after the  
28 use of the UV-curing polish; they were patch tested at five dermatology clinics Sweden. It  
29 was shown that all 8 patients showed contact allergic reactions towards Di-HEMA-TMHDC.  
30

31 Geier (2016) performed a study on dental technicians with occupational dermatitis. Di-  
32 HEMA-TMHDC has been patch tested in this series in 6775 patients during the years 2008 to  
33 2015 (total number of patients: 99,130). 47/6775 (0.7%) patients showed a reaction. Thus,  
34 it was the least frequent allergen among the (meth-)acrylates in this series. Therefore, the  
35 authors concluded that there is no conclusive indication that Di-HEMA-TMHDC represents a  
36 special, frequent, or particularly severe allergological problem, compared to other  
37 methacrylates.  
38

40  
41 **SCCS comment on human (patch-test) studies with Di-HEMA-TMHDC**

42 There are only a few reports with information on sensitisation to Di-HEMA-TMHDC among  
43 users of nail-styling products. Di-HEMA-TMHDC is commonly used in dentistry and more  
44 reports are available from this professional group. The LLNA indicates that it is a weak  
45 sensitisier. This is reflected in the clinical studies in humans, especially the study among  
46 dental technicians (Geier 2016) which indicates that this was the least frequent allergen  
47 among the acrylates. The human studies do not indicate that sensitisation to Di-HEMA-  
48 TMHDC is of concern among users of nail-styling products.  
49

50 **Respiratory effects among professional users**

51 Several epidemiological studies among professionals applying and sculpturing artificial nails  
52 point towards an increased risk of asthma (Kreiss 2006; Reutman 2009; Roelofs 2008). A  
53 clinical study with simulated inhalation exposure to nail-styling work using different  
54 acrylates among two professionals with asthmatic complaints established occupational

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1 asthma (Sauni 2008). Interestingly, one of these cases had also been diagnosed with  
2 allergic contact dermatitis with contact sensitisation to 2-HEMA and to ethylene glycol  
3 dimethylacrylate (EGDMA). Three out of 10 nail-stylists with occupational allergic contact  
4 dermatitis to acrylates experienced exacerbation of pre-existing asthma (Lazarov 2007). In  
5 a study among 71 nail stylists who responded to an invitation for a clinical respiratory  
6 examination, rhinitis (in 21%) was detected, as well as an overall tendency to reduced  
7 expiratory flow (FEV) and diffusion (Dessalces 2014).

8

9

10 **3.3.12 Discussion**

11

12

13 **Physicochemical properties**

14

15 Data on the impurities in HEMA and Di-HEMA-TMHDC, in particular the presence of possible  
16 sensitisers, have not been provided.

17 Additional information on the stability studies (conditions, any stabiliser added, analytical  
18 method used to evaluate stability) is not provided.

19 Information on the speed and completeness of the polymerisation and persistence of Di-  
20 HEMA-TMHDC monomer under use conditions along with information on the concentration  
21 and the type of polymerisation inhibitors and polymerisation activators is not provided.  
22 Information on various commercial systems used for polymerising HEMA and Di-HEMA-  
23 TMHDC is also not provided.

24

25 **Nail penetration**

26

27 Penetration of the nails by pharmaceuticals (mainly anti-fungal agents) has generally been  
28 insufficient to deliver the desired dosage. Several studies show that the nail plate behaves  
29 like a hydrophilic-gel barrier and is not lipophilic (Mertin 1997, Brown 2009, Kobayashi  
30 2004, Kobayashi 1999). Nail permeability is however independent of lipophilicity, but clearly  
31 decreases with increasing molecular weight (Kobayashi 2004). Flux through the nail plates  
32 of caffeine, methylparaben and Terbenafine are in the order of 0.55 to 6.5 microgram per  
33 cm<sup>2</sup> per hour (Brown 2009). The flux of p-Hydroxybenzoic acid methyl ester -  
34 methylparaben - (which has a molecular weight close to that of HEMA) was estimated to be  
35 approx. 15 microgram per cm<sup>2</sup> per half a day (Kobayashi 2004).

36 In view of these studies, and considering that polymerisation is initiated immediately after  
37 application, it can be assumed that monomers of HEMA and di-HEMA-TMHDC penetrate the  
38 nails only in negligible amounts. In view of the moderate sensitisation potency, it can also  
39 be assumed that induction of sensitisation is unlikely from the very small amounts that  
40 could theoretically be presented to the immune system at the level of the nail bed.

41

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

46

47 **Sensitisation**

48

49 **HEMA**

50 The animal studies indicate that HEMA can be considered as an allergen with weak to  
51 moderate potency.

52 The human studies conducted by patch testing among patients in dermatology clinics  
53 indicate that this substance can be considered an allergen of concern. However it should be  
54 noted that among consumers the sensitisation most likely results from contamination of the  
55 skin adjacent to the nails (with a relatively short exposure to a high concentration) because

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1 penetration through the nail plate is likely to be negligible. This means that application that  
2 is restricted to the nail plate is safe.  
3 Compared to the consumers (those having their nails treated), the potential for sensitisation  
4 to HEMA is considerably higher amongst the professional users when protective measures  
5 are neglected. The clinical studies (in patch-tested populations) support this. Besides skin  
6 exposure due to inadequate handling of the monomers, the removal of excess nail-polish  
7 material using unprotected fingers is also likely to occur.  
8 It should also be noted that the data obtained in clinical studies do not reflect the real  
9 incidence in the general population of HEMA contact allergy, which is at the moment  
10 unknown. An increase in incidence may occur due to the increasing popularity of artificial  
11 nails.  
12

13 *Di-HEMA-TMHDC*

14 There are only a few reports with information on sensitisation to Di-HEMA-TMHDC among  
15 users of nail-styling products. Di-HEMA-TMHDC is commonly used in dentistry. The LLNA  
16 indicates that it is a weak sensitisier. This is reflected in the clinical studies in humans. The  
17 human studies do not indicate that sensitisation to Di-HEMA-TMHDC is of concern among  
18 users of nail-styling products.  
19

20 Respiratory problems have been reported among professional users of nail-styling products,  
21 but the causative chemicals are often not identified.  
22 For 'metacrylates' the evidence for respiratory allergy was denoted as limited or  
23 contradictory in one review (Baur 2013) and absent in an updated version (Baur 2014).  
24

25 For professional users, guidelines for the prevention of skin sensitisation and respiratory  
26 problems are available (NIOSH 2011). A recent report from the French Authorities (ANSES  
27 2017) reviews and discusses a range of exposures to various chemicals in nail-styling  
28 professionals.  
29

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1

2 **4. CONCLUSION**

3

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

7

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

17

18

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

21

- 22 • More analytical data are needed to exclude the possibility of the presence of other  
23 sensitisers that may be present as impurities or degradation products alongside the  
24 two methacrylate monomers.
- 25 • Both HEMA and di-HEMA-TMHDC are weak to moderate sensitisers and may pose a  
26 risk of sensitisation from misuse of the products or from inappropriately carried out  
27 application that may lead to skin exposure.
- 28 • Filing or sanding nails to remove/replace previous applications may generate particle  
29 dust that may lead to respiratory exposure of the professionals if appropriate  
30 protective measures are not in place.
- 31 • The potential for sensitisation to the methacrylate monomers is likely to be higher  
32 amongst the professionals who carry out routine applications of artificial nail  
33 modelling systems.
- 34 • In view of the growing popularity of artificial nail fashions, and the potential use by  
35 consumers at home, any increase in future incidence of sensitisation should be kept  
36 under surveillance.

37

38

39 **5. MINORITY OPINION**

40 /

41

42

43

44

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## Opinion on the safety of cosmetic ingredients HEMA (CAS 868-77-9) and Di-HEMA Trimethylhexyl Dicarbamate (CAS 41137-60-4 / 72869-86-4) - Submission I (Sensitisation only)

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