Substance Name: Hexamethylene diacrylate (hexane-1,6-diol diacrylate)

EC Number: 235-921-9

CAS Number: 13048-33-4

SUPPORT DOCUMENT TO THE OPINION OF THE MEMBER STATE COMMITTEE FOR IDENTIFICATION OF HEXAMETHYLENE DIACRYLATE (HEXANE-1,6-DIOL DIACRYLATE) AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE DUE TO ITS SKIN SENSITISING PROPERTIES, IT CAUSES PROBABLE SERIOUS EFFECTS TO HUMAN HEALTH WHICH GIVE RISE TO AN EQUIVALENT LEVEL OF CONCERN TO THOSE OF CMR[1] AND PBT/vPvB[2]

Adopted on 10 December 2015

[1] Carcinogenic, mutagenic and toxic for reproduction.
[2] Persistent, bioaccumulative and toxic or very persistent, very bioaccumulative

CONTENTS

TABLES

ABBREVATIONS

Bis-MA	1,3-Butylene glycol dimethacrylate
BUDA	1,4 –butandiol diacrylate
BUDMA	1,4-Butanediol dimethacrylate
DEGDA	Diethylene glycol diacrylate
DEGDMA	Diethylene glycol dimethacrylate
DNEL	Derived No Effect Level
DPGDA	Dipropylene glycol diacrylate
ELoC	Equivalent Level of Concern
GMA	Glycidyl methacrylate
GPMT	Guinea Pig Maximization Test
HDDA	Hexamethylene diacrylate
MSDS	Material Safety Data Sheet
NPGDA	Neopentyl glycol diacrylate
PETA-3	Pentaerythritol triacrylate
PETA-4	Pentaerythritol tetraacrylate
TEGDA	Tetraethylene glycol diacrylate
TPGDA	Tripropylene glycol diacrylate
TMPTA	Trimethylolpropane triacrylate
TREGDA	Triethylene glycol diacrylate
TREGDMA	Triethyleneglycol dimethacrylate

GLOSSARY

Allergic contact dermatitis	A form of contact dermatitis. The clinical manifestation of a changed responsiveness of the immune system following repeated exposure to a sensitising substance
Antigen presenting cells	A heterogeneous group of immune cells that mediate the cellular immune response by processing and presenting antigens to the T-helper cells.
Cross-reaction	An allergic reaction to an antigen that is chemically similar to the sensitising antigen.
Cytokines	Cell signalling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma.
Dermatitis	A general term that describes an inflammation of the skin. It usually involves redness (erythema), swelling (papules and oedema) and blisters (vesicles). Contact dermatitis is an inflammatory skin reaction due to noxious agents in the environment.
Effector T-cells	Specialised T cells that target specific antigens.
Elicitation phase	Production of an allergic response that occurs when a sensitised individual is re-exposed to an allergen or a cross reacting allergen, resulting in clinically visible disease, allergic contact dermatitis.
Erythema	Skin condition characterised by redness and/or rash.
Immunological memory	The ability of the immune system to respond more rapidly and effectively to an antigen that has previously been encountered.
Induction phase	Alteration of the immune status of an individual, following skin exposure to a contact allergen. The exposed individual develops a specialized immunological memory and can respond rapidly on repeated exposures (also called sensitisation phase).
Keratinocytes	The predominant cell type in the skin, involved in allergic responses by producing cytokines.
Langerhans cells	Antigen presenting immune cells in the skin.
Memory T-cells	T-cells that retain a memory of an antigen after the initial exposure and rapidly expand to a large number of effector T-cells upon re-exposure.
Patch test	The standard procedure to diagnose contact allergy. Also called epicutaneous test. Allergens are applied under occlusion on the skin, normally for two days, to determine if an allergic response (positive patch test reaction) occurs.
Sensitised individual	A person that has acquired a heightened immunologic responsiveness to an allergen.
Skin sensitiser	A substance that may lead to sensitisation and allergic response following skin contact. Also called allergen, antigen or hapten in this context.
T-helper cells	A type of T cell that regulate the activity of other immune cells by releasing cytokines. These cells are for example essential in the activation and growth of cytotoxic T cells.
Toxic Epidermal Necrolysis	A severe skin disorder characterised by widespread erythema, skin necrosis, blisters and skin detachment on more than 30 % of the body surface, leaving the body susceptible to severe infection. In severe cases the extensive skin loss can cause sepsis and even be life threatening.

IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance Name: Hexamethylene diacrylate (hexane-1,6-diol diacrylate) (HDDA)

EC Number: 235-921-9

CAS number: 13048-33-4

The substance should be identified as a substance of equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of Regulation (EC) No 1907/2006 (REACH) according to Article 57(f) of REACH Regulation.

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

In order to identify a substance as a SVHC under Article 57(f) of Regulation (EC) 1907/2006 (REACH), an equivalent level of concern (ELoC) assessment must be carried out showing that there is scientific evidence of probable serious effects to human health or the environment which give rise to an ELoC to those of other substances that fulfil the criteria in REACH Article 57(a-e). HDDA is considered to fulfil the criteria

Classification and potency

Hexamethylene diacrylate (hexane-1,6-diol diacrylate) (HDDA) is covered by index number 607-109-00-8 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified as Skin Sensitiser Category 1.

Data from studies in animals (Guinea pig maximization tests) show that HDDA is a skin sensitiser of high potency that fulfils the CLP classification criteria as Skin Sens. 1 A. The available data from human epidemiological studies and clinical case reports also suggest that HDDA is a strong sensitiser. The only cross-sectional workplace study on HDDA shows a high frequency of sensitisation among exposed individuals. Five out of 81 individuals (6.2 %) who handled an acrylic glue in their daily work were sensitised to HDDA and suffered from allergic contact dermatitis. In addition, several retrospective studies at dermatology clinics in the EU show that >2% of the patients test positive for HDDA depending on the selected patient group. Due to cross-reactivity it cannot be ruled out that the induction of sensitisation, in some cases, was caused by other acrylates.

Reported effects on human health

The following case reports describe people who suffer from allergic contact dermatitis to HDDA from exposures to UV-cured inks in the printing industry and sought medical care for their problems. The reported cases show that the symptoms may appear after a single exposure or after longer periods of exposure and may vary in severity. In severe cases, the condition involves blistering and disrupted skin integrity and in one very severe case, the lesions spread outside of the exposed area and required hospital care. In the following cases, the authors have identified HDDA as the one or one of the most likely causes of the sensitisation.

- A 33-year old woman who worked in the printing industry developed allergic contact dermatitis that later progressed into a very severe skin reaction, manifested as severe diffuse erythema with skin detachment and blisters on the extremities, face and abdomen that extended outside of the exposed area (Ido, Kiyohara et al. 2012). The woman was initially treated with topical glucocorticoids and then with oral glucocorticoids but her condition worsened. When the lesions involved more than 30%

of the body the woman was admitted to hospital care where she was treated with higher doses of glucocorticoids. At the hospital, her condition gradually improved and the glucocorticoids were withdrawn after two weeks of treatment. The woman quit her job and the symptoms had not recurred at a six-month follow up. The patient was patch tested to the ingredients of the printing inks and to the Japanese standard series. The patient showed positive patch test reaction to HDDA that progressed and was extremely strong one week after the test (+++). The patient also showed positive test reactions to a blend of HDDA and urethane acrylate (+), propoxylated neopentyl glycol diacrylate (++) and nickel sulphate (+). The woman was diagnosed with toxic epidermal necrolysis (TEN) due to exposure to UV-cured inks. The diagnosis was based on her clinical symptoms and histopathological examinations, both at the site of the allergic lesions and at the site of the positive patch test to HDDA. TEN is characterised by widespread erythema, necrosis, blisters and skin detachment on more than 30 % of the body surface, leaving the body more susceptible to infections. It is a very severe but rare skin disorder that may even be life threatening.

- A 50-year old man who was exposed to two acrylic products in his work in the printing industry developed what was described by the authors as very severe bullous allergic contact dermatitis after three years at the work-place (Vogel & Schuttelaar, 2013; Vogel, Christoffers et al. 2014). The two products contained 93 % HDDA and 97 % glycidyl methacrylate (GMA) respectively. The reactions started with mild eczema on the knee, fingers and wrists that developed into tense blisters within 24 hours. The lesions healed without scar formation within 10 days. The man showed strong positive patch test reactions (+++) to HDDA and GMA and also to a number of other acrylates that had not been identified as components of the glue. Since HDDA and GMA accounts for the major exposures and gave a strong patch test response, the authors identify these substances as the most likely cause of the reaction. According to the authors the positive patch tests to other acrylates are likely attributed to cross-reactivity or concomitant sensitisation to acrylates not stated in the (M)SDS.

- A 50-year old man working in the printing industry developed a severe allergic skin reaction after a work place accident were he spilled a bucket of effluent from the printing process over himself (Morgan and Fewings 2000). The authors described the condition as severe allergic contact dermatitis. The allergic reaction appeared ten days after the accident, when the man put on the same trousers as he had worn at the time of the accident. Within a couple of hours, he got a burning sensation that later developed into severe dermatitis at the buttocks. HDDA was one of the main acrylates used in the factory and patch tests later showed that the patient was sensitised to a number of acrylates including HDDA (++).

- A 51-year old man working in the printing industry developed hand dermatitis a few weeks after he had started to handle UV-cured acrylates in his work (Morgan and Fewings 2000). The patient showed positive patch test reactions to HDDA (++) and the HDDA primed plastic coated sheet he was exposed to (+). He did not show positive patch test to any of the other twenty-three acrylates he was tested for. According to the case report, the man kept on being exposed to the priming agent at work and consequently, he continued to suffer from hand dermatitis.

Five cases of beauticians who suffer from allergic contact dermatitis and show positive patch tests to HDDA have been reported in the literature (Cravo, Cardoso et al. 2008, Roche, de la Cuadra et al. 2008, Pesonen, Kuuliala et al. 2012, Kiec-Swierczynska, Krecisz et al. 2013). The exact compositions of the acrylic glues are not revealed in these reports and the authors have not tried to identify the most likely cause of the allergic reactions. The described symptoms involve for example eczema, oozing lesions, and blisters of the hands and face and irritation in nose and eyes. It was reported that the patients had to change work tasks or profession and some of the patients experienced recurring symptoms in their new work as they again were

exposed to acrylic compounds.

Equivalent level of concern assessment

In order to identify a substance as a SVHC under REACH Article 57(f) an ELoC assessment must be carried out showing that there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances that fulfil the criteria in REACH Article 57(a-e). The ELoC assessment for HDDA was carried out as described in ECHA's general approach for identification of SVHC under article 57(f) considering the following factors together in one package for all endpoints, rather than making comparisons one factor at a time (ECHA 2012).

Type and severity of possible health effects

The ECHA discussion paper describes severe skin damage as follows *"e.g. blistering that can burst. Skin function (integrity) is impaired, possibly leading to infection. Ongoing exposure can lead to chronic inflammation and scar formation. Minimal or a single small focus of scarring does not normally constitute "severe organ damage or major permanent functional change" in the skin as an organ."*

Data from experimental animal studies and studies in humans show that non-cured HDDA is a very potent skin sensitiser that can cause sensitisation manifested as mild to very severe allergic contact dermatitis (Morgan and Fewings 2000, Constandt, Hecke et al. 2005, Kiec-Swierczynska, Krecisz et al. 2005, Goon, Isaksson et al. 2006, Teik-Jin Goon, Bruze et al. 2007, Aalto-Korte, Alanko et al. 2008, Ido, Kiyohara et al. 2012, Christoffers, Coenraads et al. 2013, Ramos, Cabral et al. 2014, Vogel & Schuttelaar, 2013, Vogel, Christoffers et al. 2014). This is supported by case reports of occupational allergic contact dermatitis to HDDA from exposure to acrylic based products, such as printing inks and artificial nail products (see above for more detailed description). The reported cases describe patients that suffer from allergic contact dermatitis of varying severity, involving erythema, bullous and oozing skin lesions and skin detachment. The case reports also show that the patients can develop symptoms after a single or few exposures, thus indicating that HDDA is a potent skin sensitiser in humans. The symptoms are most often located to the exposed areas, usually hands and arms and sometimes the face, but may also spread to other parts of the body. The affected skin has a disrupted barrier function making it more susceptible to other hazardous substances and to microbial infections. Most notable is one patient that developed toxic epidermal necrolysis (TEN), after occupational exposure to printing inks containing HDDA. The patient suffered from severe skin lesions covering more than 30% of the body and that required hospital care.

In conclusion, HDDA has the capacity to cause severe skin damage in humans. These effects involve blistering and disrupted skin integrity, as described in the ECHA discussion paper. It can be assumed that prolonged exposures to HDDA may lead to permanent skin damage, such as scarring. It is noted that CMR SVHC substances can cause adverse effects with a broad range of severity.

Irreversibility of health effects

The ECHA discussion paper states: *"In the case of skin sensitisers, the induction phase of sensitisation is irreversible, however the organ dysfunction resulting from elicitation is generally seen to be reversible i.e. the allergic reaction by the skin disappears when exposure to the sensitising agent is eliminated. In some instances, skin sensitisers can induce irreversible lesions (e.g. large lesions on the skin, leaving permanent scars and/or discoloration of the skin). However it is unusual to see irreversible damage at an early stage."* Further, it is stated that *"one could argue that the irreversible sensitisation induction is in fact an adverse effect, as it leads to a disposition of the sensitised individuals."*

It is generally acknowledged that the induction phase of sensitisation is an irreversible effect as the immunological system has been permanently modified. The elicitation phase on the

other hand is usually reversible if all exposure stops. Persons experiencing severe allergic dermatitis may need medical treatment. A sensitised person can no longer be exposed to even low concentrations of the sensitising allergen, or other cross-reacting substances, without the risk of developing a severe allergic skin reaction. Thus, a person who is sensitised to HDDA can only be free from symptoms if he or she can completely avoid exposures to HDDA and other cross-reacting acrylates. In addition, in severe cases the allergic reaction may lead to permanent skin damage.

Indeed, the case reports on HDDA describe patients experiencing recurring symptoms following repeated exposures. The allergic reactions are of such severity that one may assume that ongoing exposure may lead to permanent skin damage, such as scarring.

A recent judgement by the Court of Justice of the European Union gives support to the conclusion that the induction phase of sensitisation should be considered irreversible[3]. The court ruled that adverse health effects of the respiratory sensitisers hexahydromethylphthalic anhydride (MHHPA) and hexahydrophthalic anhydride (HHPA) may be considered irreversible because the induction phase of an allergy is irreversible and it cannot be ruled out that prolonged exposure to the anhydrides can lead to irreversible effects, namely permanent lung damage. Since the development of allergic skin reactions occur according to similar principles as allergic lung reactions, i.e. involving an immunological irreversible induction phase followed by an elicitation phase, the skin sensitising effects of HDDA should also be considered irreversible. Also for allergic contact dermatitis it cannot be ruled out that prolonged skin exposure may lead to permanent skin lesions such as scaring.

In conclusion, the skin sensitising effect of HDDA (initiation phase) is irreversible whereas the allergic skin reactions (elicitation phase) are in general reversible provided that the exposures stop. However, prolonged exposures to HDDA may cause irreversible skin damage, such as scarring.

Delay of health effects

In cases where the relationship between exposure and health effect is abstruse, for example because of a substantial delay between exposure and effect, the level of concern about the substance may be elevated (Basketter and Kimber 2014). The health effects of skin sensitisers can be delayed in two ways. First, sensitisation is not always immediate. It usually requires repeated exposures and may take weeks to years to develop. Second, because the actual sensitisation is asymptomatic, the affected individuals do not know that they have become sensitised until an allergic reaction is elicited. Reports show that it in some cases may take years from the initial exposures to HDDA until the patient develops allergic contact dermatitis, making it difficult for workers to take precautionary actions in time to avoid development of sensitisation (Morgan and Fewings 2000, Ido, Kiyohara et al. 2012, Vogel, Christoffers et al. 2014).

In conclusion, as for CMR substances there may be long/medium delays between the start of the induction phase to HDDA and appearance of clinical symptoms.

Derivation of a safe level of exposure

The ECHA discussion paper states that *"in the context of the 'equivalent level of concern' debate it is felt that an inability to derive a safe concentration may warrant a higher 'level of concern' being associated with the substance in question."*

Skin sensitisation is in principle regarded as a threshold effect, although in practice it may be very difficult to determine a safe level for human exposure (ECHA 2013). Currently there are no available dose-response data from studies in animals or humans that support determination of a quantitative DNEL for HDDA, as is also concluded in the REACH registration dossier. This means that all exposures to HDDA may increase the risk for sensitisation and that safe conditions of use may be difficult to establish.

[3] JUDGMENT OF THE GENERAL COURT (Fifth Chamber), Case T-135/13, 30 April 2015

Quality of life

The ECHA discussion paper states that *"serious impairment of a person's quality of life does not play a role in identifying a substance as an SVHC, however in the context of the 'equivalent level of concern' debate it is felt that such impairment warrants a higher 'level of concern' being associated with the substance in question."* It is further stated that *"In the case of both respiratory sensitisers and skin sensitisers, once a person is sensitised to an allergen in the workplace (e.g. hairdressers who become sensitised to hair dye ingredients), the person's exposure to that substance needs to be eliminated. In most cases, this means that the person cannot work in their chosen profession any more. Re-training may then be needed, which can lead to a significant impact on that person's quality of life."*

The overall data show that HDDA can cause occupational contact dermatitis, a condition recognized to have a negative impact on quality of life that can be directly related to the physical symptoms and also to anxiety caused by technical and social difficulties at work and the risk of losing their jobs (Skoet, Zachariae et al. 2003, Benyamini, Goner-Shilo et al. 2012, Boehm, Schmid-Ott et al. 2012). The affected persons must be removed from all exposures to HDDA, and to cross-reacting acrylates, which means that retraining may be needed, and they may not be able to work in their chosen profession. In addition, cross-reactivity between HDDA and other acrylates aggravates this problem further as it may be more difficult to find a new suitable job and to avoid exposure in everyday life. Several case reports of occupational allergic contact dermatitis caused by HDDA describe patients who experience difficulties at work that are associated with a negative impact on quality on life.

Societal concern:

The ECHA discussion paper states that *"Societal concern does not play a role in identifying a substance as an SVHC, however in the context of the 'equivalent level of concern' debate it is felt that significant societal concern may warrant a higher 'level of concern' being associated with the substance in question."*

The overall data show that HDDA can cause occupational contact dermatitis, which is recognized as a common condition with a heavy socioeconomic impact involving large costs related to a reduced productivity at work, retraining of the affected individuals, sick leave and health care (Diepgen, Scheidt et al. 2013, Saetterstrom, Olsen et al. 2014). However, there are no reliable data describing how common occupational contact dermatitis to HDDA, or to acrylates in general, is in the EU. It is therefore not possible to do accurate estimations of the societal costs from contact allergy to HDDA. In addition, the increasing use of HDDA, both in terms of volumes and products on the EU market, indicates that the problems will increase in the future if no regulatory actions are taken to minimize the risks.

Registration dossiers submitted for the substance: Yes

PART I

Justification

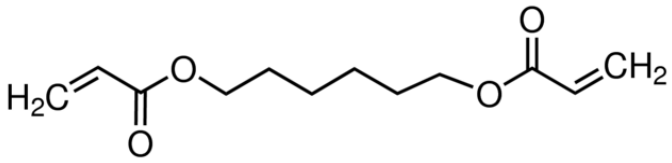
1. Identity of the substance and physical and chemical properties

1.1. Name and other identifiers of the substance

Table 1: Substance identity

EC number:	235-921-9
EC name:	hexamethylene diacrylate
CAS number (in the EC inventory):	13048-33-4
Deleted CAS numbers:	74872-03-0 88250-32-2 106717-06-0 126038-89-9 174845-65-9 181826-08-4 198694-76-7 671774-75-7 1220287-86-4
CAS name:	2-Propenoic acid, 1,6-hexanediyl ester
IUPAC name:	hexane-1,6-diyl bisacrylate
Index number in Annex VI of the CLP Regulation	607-109-00-8
Molecular formula:	$C_{12}H_{18}O_4$
Molecular weight range:	226.27 g/mol
Synonyms:	Hexanediol diacrylate, 2-Propenoic acid, 1,6-hexanediyl ester hexane-1,6-diol diacrylate

Structural formula:



1.2. Composition of the substance

Name: hexamethylene diacrylate

Description: Clear colourless liquid

Substance type: mono-constituent

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
hexamethylene diacrylate *EC no.: 235-921-9*	91.8 % (w/w)	≥ 80.0 % - 100 % (w/w)	

1.3. Identity and composition of degradation products / metabolites relevant for the SVHC assessment

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

1.4. Identity and composition of structurally related substances (used in a grouping or read-across approach)

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

1.5. Physicochemical properties

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

2. Harmonised classification and labelling

Table 3: Classification according to Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
607-109-00-8	hexamethylene diacrylate hexane-1,6-diol diacrylate	235-921-9	13048-33-4	Skin Irrit. 2 Skin Sens. 1 Eye Irrit. 2	H315 H317 H319	GHS07 Wng	H315 H317 H319			D

- H315: Causes skin irritation
- H317: May cause an allergic reaction
- H319: Causes serious eye irritation

- Note D - Certain substances which are susceptible to spontaneous polymerisation or decomposition are generally placed on the market in a stabilised form. It is in this form that they are listed in Part 3. However, such substances are sometimes placed on the market in a non-stabilised form. In this case, the supplier must state on the label the name of the substance followed by the words 'non-stabilised'

3. Environmental fate properties

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4. Human health hazard assessment

4.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.2. Acute toxicity

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.3. Irritation

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.4. Corrosivity

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.5. Sensitisation

4.5.1. Skin

HDDA is a skin sensitiser with a harmonized classification as Skin Sens. 1 (EC) No 1272/2008. Humans that are directly exposed to non-cured HDDA can become sensitised to the substance and develop symptoms of allergic contact dermatitis following repeated exposures. The skin sensitising effects of HDDA as well as other acrylates are explained by the general mechanisms for sensitisation and allergic contact dermatitis (Peiser, Tralau et al. 2012, Sasseville 2012). No mechanistic studies appear to have been conducted that specifically address the toxicological mode of action for HDDA.

Allergic contact dermatitis is the clinical manifestation of a changed responsiveness of the adaptive immune system following repeated exposure to a sensitising substance (OECD 2015). The development of allergic contact dermatitis is characterised by two distinct phases, induction phase and elicitation phase:

1. Induction phase: The first phase is the induction of specific immunological memory in an individual following dermal exposure to an antigen, i.e. the individual becomes sensitised. Dermal exposure to skin sensitising antigens, for example a chemical substance, leads to an unspecific activation of keratinocytes to release inflammatory cytokines. In addition, the antigen binds to and triggers specific activation of antigen presenting cells (Langerhans cells) in the skin. The activated Langerhans cells migrate to the lymph nodes were they present the antigen to T-helper cells. The activated T-helper cells differentiate to specialized memory T-cells and effector T-cells that migrate to the skin where they await reactivation. The induction phase is sometimes referred to

as sensitisation phase.

2. Elicitation phase: When the skin is exposed to the sensitising antigen, or a cross reacting substance, the specialized T-cells initiate a rapid and specific allergic response. T-cells migrate to the skin, where they release cytokines and recruit other inflammatory cells. These events lead to tissue inflammation characterised by oedema, erythema, scaling, and blistering. Usually, very low exposure levels are required to elicit an allergic reaction compared to the concentrations needed for induction of sensitisation.

The induction phase is irreversible and most often asymptomatic, however the adverse effects resulting from elicitation are generally reversible i.e. the allergic reaction by the skin disappears when exposure to the sensitising agent is eliminated. In some instances, skin sensitisers can induce irreversible lesions (e.g. large lesions on the skin, leaving permanent scars and/or discoloration of the skin).

4.5.1.1. Non-human information

The skin sensitising effects of HDDA have been investigated in two animal studies. The studies are included in the REACH registration dossier and form the basis for the harmonized classification of HDDA as Skin Sens. 1.

1. Guinea pig maximization test, (Bjorkner 1984): A Guinea pig maximization test (GPMT) was performed according to OECD Guideline 406 using 15 animals in the test group and 15 animals in the control group. The test group received a first intradermal induction dose with 1% HDDA in olive oil/acetone and, one week later, a second epicutaneous induction dose with 25 % HDDA in petrolatum. The control group received vehicle only. Two weeks after the first induction, all animals were given a first challenge dose and, after additional 48 hours, a second challenge dose. The challenge doses contained 0.2 % HDDA in petrolatum. The results showed that nine animals (60%) in the test group had a positive reaction after receiving the second challenge dose. No animals in the control group reacted positive to the first or the second challenge dose. The study also investigated cross-reactivity with other acrylates by giving the animals challenge doses with 1,4-butandioldiacrylate (BUDA), diethyleneglycoldiacrylate (DEGDA), tetraethyleneglycoldiacrylate (TEGDA), tripropyleneglycoldiacrylate (TPGDA), neopentylglycoldiacrylate (NPGDA). Positive reactions, indicating cross-reactivity, were seen with BUDA (1/15 animals), DEGDA (4/15 animals) and TEGDA (4/15 animals).

2. Guinea pig maximization test, (Clemmensen 1984): A supporting GPMT study following the OECD 406 guideline showed similar results as Björkner et al. The study included two test groups, with 40 and 16 animals respectively, and one control group with 20 animals. The test groups received a first intradermal induction dose with 1% HDDA in olive oil/acetone and, one week later, a second epicutaneous induction dose with 25 % HDDA in petrolatum. The control group received vehicle only. Three weeks after the first induction, the test groups were given a challenge dose with 0.3 % or 0.5 % HDDA. In the group that received a 0.3 % HDDA challenge dose, 16 out of 40 animals (40 %) showed a positive reaction. In the group that received a challenge dose with 0.5 % HDDA, 14 out of 16 animals (88 %) showed a positive reaction. None of the animals in the control group displayed a positive reaction after receiving a challenge dose with 0.3 % HDDA.

A substance fulfils the criteria for Skin Sens. 1A if ≥ 60 % of the animals in a GPMT have a positive reaction after an induction dose of > 0.1 % to ≤ 1 % of the test substance. The animal studies described above show that an induction dose of 1 % HDDA resulted in 40 %, 60 % or 88 % of positive reactions in the test groups depending on the challenge dose. Thus, animal data indicate that HDDA is a very potent skin sensitiser and fulfils the CLP criteria for classification as Skin Sens. 1A.

4.5.1.2. Human information

CLP skin sensitisation sub-categorization

According to the CLP criteria (3.4.2.2.2.1.) human evidence for sub-category 1A can include diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure. A positive patch test reaction proves that the individual is allergic to the substance in this case HDDA, and that he or she is able to develop allergic skin reactions after skin exposure to the substance (Johansen, Aalto-Korte et al. 2015). The guidance values for the frequency of skin sensitisation for classification as Skin Sens. 1A varies depending on study design (Table 3.4.2-b, Guidance on the Application of the CLP Criteria, version 4.1, June 2015). A frequency of ≥1.0 % in cross-sectional work-place studies with relatively low exposure indicates classification as Skin Sens. 1A. whereas the corresponding value for studies of selected dermatology patients with a relatively low exposure is ≥ 2.0% (Tables 3.4.2-b-d, Guidance on the Application of the CLP Criteria, version 4.1, June 2015).

One cross-sectional work-place study shows that workers who had been exposed to an acrylic glue were sensitised to acrylates and suffered from allergic contact dermatitis (Kiec-Swierczynska, Krecisz et al. 2005). The workers reacted most frequently to TREGDA (12.5 %), DEGDA (11.2 %), HDDA (6.2 %) and BUDA (5.0 %). However, none of these acrylates were included in the (M)SDS for the glue, suggesting incomplete information. Several studies of selected patient groups at dermatology clinics also indicate a high frequency of sensitisation for HDDA as they report positive diagnostic patch test reactions in more than 2 % of the patients (Constandt, Hecke et al. 2005, Goon, Isaksson et al. 2006, Teik-Jin Goon, Bruze et al. 2007, Aalto-Korte, Alanko et al. 2008, Christoffers, Coenraads et al. 2013, Ramos, Cabral et al. 2014). Thus, these studies show a relatively high frequency of occurrence of skin sensitisation. However, in order to subcategorise human diagnostic patch test data information on exposure is needed (CLP art 3.4.2.2.2.1 b).

In summary, data from studies in animals show that HDDA is a potent skin sensitiser that fulfils the CLP classification criteria as Skin Sens. 1 A. In humans, high severity of responses might be used as an indication that classification as Category 1A is appropriate, for example where the substance has caused hospitalisation due to acute skin reaction or generalised (systemic/whole body) dermatitis (Guidance on the Application of the CLP Criteria, version 4.1, June 2015). One case study (Ido, Kiyohara et al., 2012) showed very severe skin reactions to HDDA supporting sub-category 1A. The available human diagnostic patch test data suggest that HDDA induces high frequency of occurrence of skin sensitisation. However, for all studies in humans it cannot be ruled out that the induction of sensitisation has been caused by other acrylates.

Updating the classification to Category 1A would enforce labelling of products containing ≥0.01% HDDA. This would allow workers to avoid lower levels of HDDA than what is currently possible. However, data from the Swedish product register indicate that most products contain ≥0.1 % HDDA. Curable inks typically contain around 30% HDDA but the content varies. Most products are therefore already subject of CLP labelling requirements and the risk reducing effects from an updated classification are expected to be minor.

Case reports

Below, a number of peer-reviewed case reports of occupational contact dermatitis associated with exposure to printing inks containing HDDA are presented.

Toxic epidermal necrolysis from UV-cured printing inks (Ido, Kiyohara et al. 2012)

A 33-year old woman who worked in the printing industry developed allergic contact dermatitis that later progressed into a very severe allergic skin reaction manifested as

severe diffuse erythema with skin detachment and blisters on the extremities, face and abdomen (Ido, Kiyohara et al. 2012). After one week at the workplace, the woman developed redness and rash on the exposed areas, hands, arms and face. She was first treated with topical glucocorticoid ointment and then with oral prednisolone for three days but the skin lesions progressed until bulla and erosion spread outside of the exposed area to cover more than 30 % of the body surface. There were no signs of mucosal involvement. The patient was then admitted to hospital care and received higher doses of prednisolone whereby her condition gradually improved. Histopathological examinations of skin biopsies showed vacuolar changes in the basal keratinocytes, satellite cell necrosis, necrotic keratinocytes, in the upper epidermis, and subepidermal blister formation. Blood examinations showed a moderate increase in white blood cells (eosinophilia) and a mild elevation in C-reactive protein. Based on her clinical history, histopathological findings, and positive patch tests to components in the UV-cured inks, the patient was diagnosed with toxic epidermal necrolysis (TEN) due to contact with ultraviolet-cured inks.

TEN is a severe skin disorder characterised by widespread erythema, necrosis, blisters and skin detachment on more than 30 % of the body surface, leaving the body more susceptible to infections (Ellender, Peters et al. 2014). Erosive mucosal lesions affecting especially the eyes, mouth, lips, and genitals may also be part of the clinical picture of TEN, but such effects were not seen in the case described above. The skin symptoms are often preceded by flu-like symptoms. In severe cases, the extensive skin loss can cause sepsis and/or death with a mortality rate of 25-30 %. The incidence is reported to be very low, 0.4-1.2 cases per million and year. A majority of the cases are associated with adverse drug reactions but there are also previous reports of work related chemical exposures leading to toxic epidermal necrolysis (House, Jakubovic et al. 1992, Kamijima, Hisanaga et al. 2007). It is considered highly unlikely that glucocorticoids should have induced the very severe reaction in the present case since high doses of glucocorticoids actually proved to be a very efficient treatment.

Patch tests and photo patch tests were performed with eight ingredients of the UV-cured inks. Positive test reactions were seen to HDDA, a blend of HDDA and urethane acrylate (+), and propoxylated neopentyl glycol diacrylate (++). The other five ink ingredients gave negative results. Additional patch tests with the 25 allergens in the Japanese standard series only showed a weak (+) positive reaction to nickel sulphate. HDDA gave the strongest patch test reaction and an extreme positive reaction (+++) on the skin that could still be observed eight days after the test was done. Histopathological examination of the site of the positive patch test to HDDA showed pronounced oedema of the papillary dermis, resulting in subepidermal blisters.

According to the patient, she was wearing goggles, gloves and protective clothing at work but despite the safety precautions, her face and arms had been exposed to UV-cured inks, and her clothing had become soaked. She later quitted her job in the printing industry and at a six-month follow-up, the symptoms had not recurred.

- Severe bullous contact dermatitis from liquid HDDA,(Vogel, Christoffers et al. 2014)
  A 50-year old man who was exposed to liquid HDDA and glycidyl methacrylate (GMA) in his work developed bullous allergic contact dermatitis, which was considered by the authors as very severe. The allergic reaction started as a skin irritation on the knee, fingers and wrists that developed into tense blisters within 24 hours. The symptoms appeared after he had been working as a process operator in the production of semi-finished products for three years (Vogel & Schuttelaar, 2013; Vogel, Christoffers et al. 2014). The lesions healed without scar formation within 10 days. HDDA and GMA gave strong positive reactions in patch tests (+++). Besides the severe reactions to the patch test materials on his back, he showed a serous crust on his forehead. This was interpreted as a recall reaction resulting from local skin memory indicating a systemic effect.

The man used two acrylic products that according to the safety data sheet contained 93% HDDA and 97% GMA, respectively. Mass spectrometry analysis showed that one product contained 93 % HDDA and 6.5% unidentified acrylates and the other product contained 97% GMA, 0.5% HDDA, 0.2% dichloropropanol and 1.7% unidentified acrylates. Since HDDA and GMA account for the major exposures, they are pointed out by the authors as the most likely cause of the allergic reaction. In addition to HDDA and GMA the patient showed positive patch tests to several other acrylates and methacrylates that were not identified in the products he was exposed to. According to the authors, these positive reactions may be explained by cross-reactivity or concomitant sensitisation to contaminating acrylates.

The man reported that he wore chemical resistant, but liquid-permeable, clothing and gloves as protection; cotton gloves with a rubber coating on the palmar sites of the gloves for use during dry activities, and thick nitrile gloves with a cotton lining when handling liquids. He changed his clothes a few times a week and his gloves once or twice a day, depending on his activities. The patient kept his work assignments but was advised to take strict protective measures against all traces of acrylates, including unnoticed spatter and spill of products containing acrylates. If handling of acrylate-containing products was inevitable, he was advised to wear impermeable, three-layered laminated gloves made of polyethylene/ethylene vinyl. Nitrile gloves were considered unsuitable for this purpose, because of their short breakthrough time.

- Severe buttock dermatitis from printing chemicals, (Morgan and Fewings 2000)
  A 50-year old man working in the printing industry spilled a bucket of effluent from the printing process over himself. The man was normally not in contact with the printing chemicals so this case describes the health effects from one single acute exposure. Ten days after the exposure the man put on the same trousers as he had worn at the time of the accident. According to the authors, the man got a burning sensation within a couple of hours that later developed into severe dermatitis. HDDA was one of the main acrylates used in the factory and patch tests later showed that the patient was sensitised to a number of acrylates including HDDA, indicating that exposure to HDDA was a likely cause of the severe effect observed.
- Hand dermatitis from an UV-cured priming agent, (Morgan and Fewings 2000)
  A 51-year old man working in the printing industry developed hand dermatitis from handling primed plastic sheets in his work. He was also exposed to the uncured priming agent, an UV-cured acrylate. His problems began a few weeks after they had started to use UV-cured acrylates at the workplace (Morgan and Fewings 2000). The patient underwent patch testing to the acrylate series and to the three plastic-coated sheets he was exposed to, one of which he in particular suspected to be the cause of the problem. The patient showed a strong positive reaction to HDDA and he also reacted positive to the suspected plastic sheet that was primed with HDDA. The patch testing was negative for all other acrylates tested. According to the case report, the man kept on being exposed to the priming agent at work and consequently, he continued to suffer from hand dermatitis.

In the following cases where beauticians showed positive patch tests to HDDA, the exact causative agents for the sensitisation were not investigated.

- Blistering and oozing eczema on hands and ears from artificial nails, (Kiec-Swierczynska, Krecisz et al. 2013)
  A woman working as a manicurist developed allergic contact dermatitis from acrylic based artificial nail products (Kiec-Swierczynska, Krecisz et al. 2013). The symptoms first appeared as redness and oozing skin lesions of the ears and external auditory canals, followed by hand eczema and bullous lesions on the fingers. Skin symptoms were accompanied by irritation in nose and eyes. The symptoms appeared after three months of work and because of her skin disorder, she had to give up her job. She later started working as a dental nurse where she was exposed to dental materials

containing acrylates. Within four months, the skin problems reappeared, obliging her to change her job again.

Patch tests showed positive reactions to six acrylates and methacrylates: HDDA, 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, ethyleneglycol dimethacrylate, triethyleneglycol dimethacrylate, 2-hydroxyethyl acrylate and triethyleneglycol diacrylate. The exact composition of the nail products was not revealed by the manufacturer.

- Hand dermatitis from artificial nails, (Pesonen, Kuuliala et al. 2012)
  A 34-year-old beautician developed allergic contact dermatitis manifested as hand eczema after she had been working with artificial acrylic nail products for four years (Pesonen, Kuuliala et al. 2012). The symptoms healed when she stopped applying artificial nails, but reappeared and became continuous when she started to work with eye lash extensions and also occasionally with artificial nails. Patch tests showed that the patient was sensitised to a large number of acrylates and methacrylates, including HDDA. The publication does not include information about the exact composition of the sensitising products.
- Nail and hand dermatitis from artificial nails, (Cravo, Cardoso et al. 2008)
  Report of four patients who developed allergic contact dermatitis from professional application and/or consumer use of artificial nails. The patients suffered from eczema around the nails and on the hands, one patient developed eyelid dermatitis. The symptoms resolved when the patients stopped working with the products or removed the artificial nails except from one patient that got persistent distal onycholysis (nail loss). Patch tests to an acrylate series including HDDA showed that all four patients were sensitised to one or more acrylates. One out of four patients showed a positive reaction to HDDA.
- Hand and face dermatitis from artificial nails, (Roche, de la Cuadra et al. 2008)
  A review of fifteen cases of allergic contact dermatitis to artificial acrylic nails diagnosed at the dermatology clinic of Valencia University Hospital in Spain from 1981-2008. Two of the patients had become sensitised to HDDA from their work as manicurists. Both patients suffered from eczema on the hands and one of them developed facial oedema.

Cross sectional work place study

- Occupational contact dermatitis from an acrylic glue, (Kiec-Swierczynska, Krecisz et al. 2005)
  A cross sectional study of workers involved in the production of electric coils for television displays reported that 9 out of 81 workers (11.2 %) suffered from allergic contact dermatitis and that five of them (6.2 %) were sensitised to HDDA (Kiec-Swierczynska, Krecisz et al. 2005). This is considered as a high frequency of sensitisation indicative for substances with a strong potency (ECHA 2015). All workers were occupationally exposed to an acrylic glue that had been used in the production for four years. The glue application and curing were automatic. Thereafter the workers manually examined the coils and dissembled defective ones. The workers used protective gloves with severed fingertips for better operative precision. The study subjects were patch tested for fourteen acrylates and five methacrylates. The workers reacted most frequently to TREGDA (12.5 %), DEGDA (11.2 %), HDDA (6.2 %) and BUDA (5.0 %), none of these chemicals was included in the (M)SDS for the glue. The high frequency of sensitisation to acrylates not included on the (M)SDS suggests that the glue may have contained acrylates not declared on the MSDS. Such findings have previously been reported in a study by Henriks-Eckerman and Kanerva (Henriks-Eckerman and Kanerva 1997).

Epidemiological studies

Currently available epidemiological studies investigating the frequency of sensitisation to HDDA in different selected patient groups in the EU is described below:

- (Ramos, Cabral et al. 2014)

  A retrospective observational study of all patients who were patch tested between January 2006 and April 2013 at the University Hospital in Coimbra, Portugal. The study included 2263 patients of which 122 underwent aimed testing with an extended series of seventeen acrylate/methacrylate series. Thirty-seven patients with mixed occupational background showed positive and relevant reactions to at least one acrylate and nine of them (7.4 %) tested positive for HDDA.

- (Christoffers, Coenraads et al. 2013)

  A retrospective observational study of 151 patients with mixed occupational background that had been patch tested with an acrylate series at the Department of Dermatology, University of Groningen between 1993 and 2012. The series contained 29 acrylates/methacrylates including HDDA. Five out of the 151 patients (3.3 %) showed a positive result for sensitisation to HDDA.

- (Geukens and Goossens 2001)

  A retrospective observational study of all patients that had been patch tested at the Dermatology department of the Katholieke Universiteit Leuven, Netherlands from 1971-1999. In total 13833 patients had been patch tested of which 31 were diagnosed with contact allergy to acrylates and three tested positive to HDDA. The article does not reveal how many of the 13388 that had been tested with the acrylate series nor to HDDA specifically.

- (Goon, Isaksson et al. 2006)

  A retrospective observational study of all patients that had been patch tested for the dental patient series or the dental personnel series (both including HDDA) at the Dermatology Department at Malmö University hospital in Sweden from 1995 to 2005. Positive patch tests to one or several acrylates were seen in 30 out of 1322 people tested with the dental patients series and in 18 out of 310 people tested with the dental personnel series. Overall, totally four out of 1632 patients (0.25 %) tested positive to HDDA.

- (Aalto-Korte, Alanko et al. 2008)

  A study of ten patients that suffered from allergic skin reactions from occupational exposures to acrylic based glues. Three of the patients showed positive patch test reactions to HDDA. Those patients who were sensitised to HDDA worked as a machinist assembler, an optician and a sewing-machine mechanic.

- (Constandt, Hecke et al. 2005)

  A retrospective observational study of 27 dermatitis patients that had been in contact with acrylic artificial nails, professional manicurists or end users. The number of acrylates that the patients were tested for varied. Eight patients were tested for contact allergy to HDDA and two of them (25 %) showed a positive result.

- (Teik-Jin Goon, Bruze et al. 2007)

A retrospective observational study of 90 patients that suffered from dermatitis suspected to be caused by acrylates. The patients had been tested with the acrylate and/or the nail acrylics series at the dermatology clinic at Malmö University Hospital in Sweden from 1995 to 2005. The patch tests showed that 24 out of 90 patients were sensitised to at least one acrylate. Twenty-one patients had been tested for HDDA of which ten (48 %) showed positive reactions.

Cross-reactions to other acrylates

The studies on HDDA and related health effects referred to in this dossier, also involve co-exposure to other acrylates. In occupational settings, it is most common to use many different acrylates and studies in humans that exclusively investigate the health effects from a specific acrylate are very rare. Many of the acrylates are structurally similar and are known to give rise to cross-reactions. Reactions due to cross-reactivity are of very high clinical relevance since skin exposure to a cross-reacting substance also may elicit severe allergic reactions. Cross-reactivity to acrylates is, however, difficult to prove in humans who generally have been exposed to more than one acrylate, particularly in the case of occupational exposure (Kanerva 2001). Cross-reactivity has been studied in guinea pigs, and the cross-reactivity pattern among diacrylates seems to be much more pronounced for TPGDA and NPGDA, than for HDDA (Bjorkner 1984).

Most patients display positive patch tests to several acrylates and it is rarely possible to elucidate whether the multiple reactions are a consequence of cross-reactivity or co-exposure to several acrylates. The fact that there may exist cross-reactivity between different acrylates and that allergic reactions to HDDA, in some cases, may be caused by sensitisation to other acrylates is not a reason for not taking regulatory measures. It should be noted that sensitisation to HDDA may also cause sensitisation allergic reactions to other acrylates. Thus, the overall problems with occupational skin sensitisation to acrylates may improve following a phasing out of the most potent ones, such as HDDA. In addition, from a regulatory point of view, cross-reactivity may in fact be seen as a factor increasing the concern, because identification and, hence, avoidance of the causative agent will be more difficult for the affected individuals.

4.5.2. Respiratory system

No studies on respiratory sensitisation from HDDA in experimental animals or human subjects appear to be available.

4.5.3. Summary and discussion of sensitisation

Skin sensitising potency of HDDA

Substances that show a high skin sensitising potency in animals and/or a high frequency of skin sensitisation in humans can be considered strong sensitisers[4]. Strong sensitisers can sensitise people at very low doses and also with shorter and less frequent exposure (ECHA 2012). HDDA was given a harmonised classification as Skin Sens. 1 before refining the classification criteria to include two subcategories, 1A and 1B. However, data from studies in animals indicate that HDDA fulfils the CLP criteria for Skin Sens. 1A and can be considered as a sensitiser with a strong potency. Studies in humans also suggest that HDDA is a strong skin sensitiser. Case reports show that HDDA can cause severe allergic skin reactions that may develop after a relatively short period of exposure. In addition, epidemiological data indicate a high frequency of sensitisation among exposed individuals. The available studies on HDDA's effects on skin sensitising potency are described in section 4.5.1.

[4] CLP Annex I Table 3.4.2: Sub-category 1A: substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.

Type and severity of health effects from exposure to HDDA

Sensitisation to HDDA is an irreversible condition typically manifested as allergic contact dermatitis. The dermatitis may differ in severity; from a mild rash located to the exposed area to lesions with blisters and skin loss that spread outside of the exposed area. The affected skin may have a disrupted barrier function making it more susceptible to other hazardous substances and to microbial infections. The symptoms can be temporary/relapsing or chronic depending on whether a correct diagnose is set and if exposure can be avoided.

ECHA discussion paper describes severe skin damage as follows *"e.g. blistering that can burst. Skin function (integrity) is impaired, possibly leading to infection. Ongoing exposure can lead to chronic inflammation and scar formation. Minimal or a single small focus of scarring does not normally constitute "severe organ damage or major permanent functional change" in the skin as an organ."*

There are several reported cases of occupational allergic contact dermatitis to HDDA of varying severity, published in peer review scientific journals. (Morgan and Fewings 2000, Ido, Kiyohara et al. 2012, Pesonen, Kuuliala et al. 2012, Kiec-Swierczynska, Krecisz et al. 2013, Vogel, Christoffers et al. 2014). One patient developed toxic epidermal necrolysis (TEN), which is a very severe, and potentially life threatening, condition that require hospital care (Ido, Kiyohara et al. 2012). In two other case reports the authors describe the allergic reactions as severe or very severe. In these cases, the authors identified HDDA as a likely cause of the allergic reaction. In addition, severe allergic contact dermatitis have been reported in beauticians, however in these cases the causative allergens were not investigated.

Prevalence of sensitisation to HDDA

HDDA is not included in the European Baseline Series[5] that is routinely used for diagnostic purposes in dermatology clinics. Therefore, patients are only patch tested for HDDA under certain circumstances, for example if they participate in a clinical study or if they undergo a more thorough clinical examination. The data about prevalence of sensitisation to HDDA is therefore scarce.

The available data indicate a high frequency of sensitisation to HDDA among exposed individuals. One study reports that 5 out of 81 workers (6.2 %) who handled an acrylic glue in their daily work had become sensitised to HDDA and suffered from allergic contact dermatitis (Kiec-Swierczynska, Krecisz et al. 2005). In addition, several retrospective studies of selected patient groups that have been tested for contact allergy to acrylates show that more than 2 % of the patients test positive for HDDA (Constandt, Hecke et al. 2005, Goon, Isaksson et al. 2006, Teik-Jin Goon, Bruze et al. 2007, Aalto-Korte, Alanko et al. 2008, Christoffers, Coenraads et al. 2013, Ramos, Cabral et al. 2014). Thus, the overall available data indicate a high frequency of sensitisation among exposed individuals, indicating that HDDA is a strong sensitiser in humans.

In total, reports published from 2000 to 2014 in the EU identified 50 patients that tested positive to HDDA in clinical patch test studies (Morgan and Fewings 2000, Geukens and Goossens 2001, Constandt, Hecke et al. 2005, Kiec-Swierczynska, Krecisz et al. 2005, Goon, Isaksson et al. 2006, Teik-Jin Goon, Bruze et al. 2007, Aalto-Korte, Alanko et al. 2008, Cravo, Cardoso et al. 2008, Roche, de la Cuadra et al. 2008, Ido, Kiyohara et al. 2012, Pesonen, Kuuliala et al. 2012, Christoffers, Coenraads et al. 2013, Kiec-Swierczynska, Krecisz et al. 2013, Ramos, Cabral et al. 2014, Vogel, Christoffers et al. 2014). Most cases are associated with occupational exposure to UV-cured inks but there are also reports of dentists and nail technicians that have become sensitised to HDDA in their work.

In conclusion

[5] The European baseline series is the guideline minimum set of allergens to which all patients should be tested. It should form a basis for developing an appropriate more extensive allergen set to investigate an individual with allergic contact dermatitis.

Studies in animals show that HDDA is a potent skin sensitiser that fulfils the criteria for classification as Skin Sens. 1A. People that are exposed to non-cured HDDA can become irreversibly sensitised to HDDA and available data indicate that the risk of becoming sensitised is relatively high. Sensitised persons typically develop allergic skin reactions upon subsequent exposures to HDDA or other cross-reacting acrylates. For cross-reactivity, see last part in section 4.5.1. The skin reactions are in some cases reported as severe. In one particularly severe case the skin dermatitis developed into toxic epidermal necrolysis (TEN), which is a rare and life threatening condition.

4.6. Repeated dose toxicity

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.7. Mutagenicity

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.8. Carcinogenicity

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.9. Toxicity for reproduction

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

4.10. Other effects

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

5. Environmental hazard assessment

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

6. Conclusions on the SVHC Properties

6.1. CMR assessment

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

6.2. PBT and vPvB assessment

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (f) of REACH.

6.3. Equivalent level of concern assessment

6.3.1. Summary of the data provided

Hexamethylene diacrylate (hexane-1,6-diol diacrylate) (HDDA) is covered by index number 607-109-00-8 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified as Skin Sens. 1. Data from animal studies (Guinea pig maximization tests) indicate that HDDA fulfils the CLP criteria for Skin Sens. 1A and can be considered as a sensitiser with a strong potency. In addition, human data indicate that exposure to HDDA is associated with a high probability of becoming sensitised and case reports show that HDDA has the capacity to cause severe allergic skin reactions in humans.

Most cases of allergic contact dermatitis to HDDA are associated with occupational exposures in industrial settings but there are also several reports of manicurists and dental personnel that have become sensitised to HDDA and developed allergic contact dermatitis in their work. The collected data indicate that the frequency of sensitisation among exposed individuals is high. One work-place study reports that 5 out of 81 individuals (6.2 %) who handled acrylic glue in their daily work were sensitised to HDDA and suffered from allergic contact dermatitis. In addition, several retrospective studies at dermatology clinics in the EU show that >2% of the patients test positive for HDDA depending on the selected patient group.

Nine reported cases have been found of patients suffering from allergic contact dermatitis to HDDA of varying severity. Four of the cases were from exposure to printing chemicals and five following exposure to glues used for artificial nails and eyelashes. The most severe case describes a woman who developed severe allergic contact dermatitis from UV-cured printing inks and was hospitalised as her condition progressed into toxic epidermal necrolysis (TEN).

6.3.2. Equivalent level of concern assessment

In order to identify a substance as a SVHC under Article 57(f) of Regulation (EC) 1907/2006 (REACH) an ELoC assessment must be carried out showing that there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances that fulfil the criteria in REACH Article 57(a-e).

The ELoC assessment for HDDA was carried out as described in ECHA's general approach for identification of SVHC under article 57(f) considering the following factors (ECHA 2012). The assessment is based on the overall available scientific data on the skin sensitising effects from HDDA. Experimental animal studies as well as clinical studies and epidemiological data were taken into consideration in the assessment. The studies are described in more detail in section 4.5.

Type and severity of possible health effects

Data from experimental animal studies and studies in humans show that non-cured HDDA is a very potent skin sensitiser that can cause sensitisation manifested as mild to severe allergic contact dermatitis (Morgan and Fewings 2000, Constandt, Hecke et al. 2005, Kiec-Swierczynska, Krecisz et al. 2005, Goon, Isaksson et al. 2006, Teik-Jin Goon, Bruze et al. 2007, Aalto-Korte, Alanko et al. 2008, Ido, Kiyohara et al. 2012, Christoffers, Coenraads et al. 2013, Ramos, Cabral et al. 2014, Vogel, Christoffers et al. 2014). This is supported by case reports of occupational allergic contact dermatitis to HDDA from exposure to acrylic based products, such as printing inks and artificial nail products. The reported cases describe patients that suffer from allergic contact dermatitis of varying severity, involving erythema, bullous and

oozing skin lesions and skin detachment. The case reports also show that the patients can develop symptoms after a single or few exposures, thus indicating that HDDA is a potent skin sensitiser in humans. The symptoms are most often located to the exposed areas, usually hands and arms and sometimes the face, but may also spread to other parts of the body. The affected skin has a disrupted barrier function making it more susceptible to other hazardous substances and to microbial infections. Most notable is one patient that developed toxic epidermal necrolysis (TEN), after occupational exposure to printing inks containing HDDA. The patient suffered from severe skin lesions covering more than 30% of the body that required hospital care.

Irreversibility of health effects

Skin sensitisation represents an irreversible adverse health effect commonly manifested as allergic contact dermatitis. A sensitised person can no longer be exposed to even low concentrations of the sensitising allergen, or other cross-reacting substances, without the risk of developing a severe allergic skin reaction. Thus, a person who is sensitised to HDDA can only be free from symptoms if he or she can completely avoid exposures to HDDA and other cross-reacting acrylates. In addition, in severe cases, the allergic reaction may lead to permanent skin damage.

Indeed, the case reports on HDDA describe patients experiencing recurring symptoms following repeated exposures. The allergic reactions are of such severity that one may assume that ongoing exposure may lead to permanent skin damage, such as scarring.

It is generally acknowledged that the induction phase of sensitisation is an irreversible effect as the immunological system has been permanently modified. The elicitation phase on the other hand is usually reversible if all exposure stops. Persons experiencing severe allergic dermatitis may need medical treatment. A recent judgement by the Court of Justice of the European Union gives support to the conclusion that the adverse health effects from sensitising substances should be considered irreversible[6]. The court ruled that adverse health effects of the respiratory sensitisers hexahydromethylphthalic anhydride (MHHPA) and hexahydrophthalic anhydride (HHPA) may be considered irreversible because the induction phase of an allergy is irreversible and it cannot be ruled out that prolonged exposure to the anhydrides can lead to irreversible effects, namely permanent lung damage. Since the development of allergic skin reactions occurs according to similar principles as allergic lung reactions, i.e. involving an immunological irreversible induction phase followed by an elicitation phase, the skin sensitising effects of HDDA should also be considered irreversible. Also for allergic contact dermatitis it cannot be ruled out that prolonged skin exposure may lead to permanent skin lesions such as scarring.

Delay of health effects

In cases where the relationship between exposure and health effect is abstruse, for example because of a substantial delay between exposure and effect, the level of concern about the substance may be elevated (Basketter and Kimber 2014). The health effects of skin sensitisers can be delayed in two ways. First, sensitisation is not always immediate. It usually requires repeated exposures and may take weeks to years to develop. Second, because the actual sensitisation is asymptomatic, the affected individuals do not know that they have become sensitised until an allergic reaction is elicited. Reports show that it in some cases may take years from the initial exposures to HDDA until the patient develops allergic contact dermatitis, making it difficult for workers to take precautionary actions in time to avoid development of sensitisation (Morgan and Fewings 2000, Ido, Kiyohara et al. 2012, Vogel, Christoffers et al. 2014).

Derivation of a safe level of exposure

Skin sensitisation is in principle regarded as a threshold effect, although in practice it may be very difficult to determine a safe level for human exposure (ECHA 2013). Currently there are no available dose-response data from studies in animals or humans that support determination

[6] JUDGMENT OF THE GENERAL COURT (Fifth Chamber), Case T-135/13, 30 April 2015

of a quantitative DNEL for HDDA, as is also concluded in the REACH registration dossier. This means that all exposures to HDDA may increase the risk for sensitisation and that a safe condition of use may be difficult to establish.

Quality of life

Patients with occupational contact dermatitis are reported to have an impaired quality of life that can be directly related to the physical symptoms and to anxiety caused by technical and social difficulties at work and the risk of losing their jobs (Skoet, Zachariae et al. 2003, Benyamini, Goner-Shilo et al. 2012, Boehm, Schmid-Ott et al. 2012). The decrease in quality of life due to contact dermatitis is reported to be similar as for psoriasis and asthma (Cvetkovski, Zachariae et al. 2006, Moberg, Alderling et al. 2009). Indeed, several case reports of occupational allergic contact dermatitis caused by HDDA describe patients who experience difficulties at work that are associated with a negative impact on quality on life.

Societal concern:

The overall data indicate that the use of HDDA in the EU is of concern for the society. The wide spread occupational exposures to HDDA may have a significant socioeconomic impact due to large costs related to a reduced productivity at work, retraining of the affected individuals, sick leave and health care from occupational allergic contact dermatitis.

Occupational allergic contact dermatitis is as a common condition with a heavy socioeconomic impact (Diepgen, Scheidt et al. 2013, Saetterstrom, Olsen et al. 2014). Saetterström et.al studied the cost-of illness of people with contact dermatitis in Denmark from four years before diagnosis to one year after. This study gives a long-term perspective on the societal costs from occupational contact dermatitis. Patients with contact dermatitis that had been seen and patch tested at dermatology clinics and where work was considered a causal or contributing factor were included in the study as cases of occupational contact dermatitis. The results showed that health care costs for people with occupational contact dermatitis were significantly higher than for matched controls. The total attributable health care cost of occupational contact dermatitis for the 5 year period was € 724 per case and the total cost for productivity loss due to sick-leave and rehabilitation was €10 722 per case for the same period. The costs attributable to occupational contact dermatitis remained constant for the first three years and increased one year before and one year after the diagnosis period. Health care costs increased from € 58 two years from diagnosis of the diagnosis to € 390 in the year after diagnosis. The productivity costs followed the same pattern but the exact yearly numbers are not given in the publication. Also, a recent study by Diepgen et.al. estimated the cost-of-illness from occupational chronic hand eczema in Germany to €8799 per person and year (Diepgen, Scheidt et al. 2013). The direct[7] and indirect[8] societal costs from contact allergy are reported to be higher for occupational exposures than for non-occupational exposures (Cashman, Reutemann et al. 2012, Diepgen, Scheidt et al. 2013, Saetterstrom, Olsen et al. 2014). The indirect costs are usually greater than the direct. Thus, this suggests that occupational contact dermatitis is a condition entailing large costs for the society.

Currently, there are no reliable data describing how common occupational contact dermatitis to HDDA is in the EU or to acrylates in general. It is therefore not possible to accurately estimate the societal costs from contact allergy to HDDA. However, the Health Safety Executive (HSE) in the UK has to some extent described the magnitude of the problem with occupational allergic dermatitis to acrylates in a report based on data from EPIDERM (Health Safety Executive (HSE) 2014). On average 76 new diagnoses of occupational contact dermatitis to acrylates and resins were reported per year in the UK in 2012-2014. Acrylates and resins were the ninth most common cause of occupational contact dermatitis in the UK, accounting for just below 5% of the cases. Soaps/cleaners and wet work constitute the most common cause.

A widespread use in high concentrations has been pointed out as a contributing factor to the

[7] Direct costs of a disease / health condition is costs primarily related to health care and medication.
[8] Indirect costs relate primarily to decreased production due to sick leave, disability, reduced productivity, or care for family.

overall evidence for identification of a substance as SVHC (Basketter and Kimber 2014). Even though susceptible individuals may become sensitised following exposure to very low concentrations of a skin sensitiser, exposures to high concentrations is associated with a greater probability for more people to become sensitised. Thus, sensitising substances that are used in higher concentrations are of greater concern. Data from the Swedish product register show that the HDDA containing products that are used in the highest volumes contain about 30% HDDA, indicating that exposure to these products are associated with a relatively large probability for becoming sensitised.

In addition, the increasing use of HDDA, both in terms of volumes and products on the EU market, indicates that the problems will increase in the future if no regulatory actions are taken to minimize the risks.

6.3.3 Conclusion on whether the substance gives rise to an equivalent level of concern

According to REACH Art. 57(f), substances for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to CMR substances (Category 1A or 1B) can be identified as SVHC on a case-by-case basis. HDDA is considered to fulfil the criteria according to Art. 57(f).

Classification and potency

Hexamethylene diacrylate (hexane-1,6-diol diacrylate) (HDDA) is covered by index number 607-109-00-8 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified as Skin Sens. 1. The ELoC assessment is based on the overall available scientific data on the skin sensitising effects from HDDA. Experimental animal studies as well as clinical studies and epidemiological data were taken into consideration in the assessment. The studies are summarised below and are described in more detail in section 4.5.

Data from studies in animals (Guinea pig maximization tests) show that HDDA is a skin sensitiser of high potency that fulfils the CLP classification criteria as Skin Sens. 1 A. The available data from human epidemiological studies and clinical case reports also suggest that HDDA is a strong sensitiser. The only cross-sectional work-place study on HDDA show a high frequency of sensitisation among exposed individuals. Five out of 81 individuals (6.2 %) who handled acrylic glue in their daily work were sensitised to HDDA and suffered from allergic contact dermatitis. In addition, several retrospective studies at dermatology clinics in the EU show that >2% of the patients test positive for HDDA depending on the selected patient group. Due to cross-reactivity it cannot be ruled out that the induction of sensitisation, in some cases, was caused by other acrylates.

Reported effects on human health

The following case reports describe people who suffer from allergic contact dermatitis to HDDA from exposures to UV-cured inks in the printing industry and sought medical care for their problems. The reported cases show that the symptoms may appear after a single exposure or longer periods of exposure and may vary in severity. In severe cases, the condition involves blistering and disrupted skin integrity and in one very severe case, the lesions spread outside of the exposed area and required hospital care. In the following cases, the authors have identified HDDA as the one or one of the most likely causes of the sensitisation.

- A 33-year old woman who worked in the printing industry developed allergic contact dermatitis that later progressed into a very severe skin reaction, manifested as severe diffuse erythema with skin detachment and blisters on the extremities, face and abdomen that extended outside of the exposed area (Ido, Kiyohara et al. 2012). The woman was initially treated with topical glucocorticoids and then with oral glucocorticoids but her condition worsened. When the lesions involved more than 30% of the body the woman was admitted to hospital care where she was treated with

higher doses of glucocorticoids. At the hospital, her condition gradually improved and the glucocorticoids were withdrawn after two weeks treatment. The woman quit her job and the symptoms had not recurred at a six-month follow up. The patient was patch tested to the ingredients of the printing inks and the Japanese standard series. The patch test reaction to HDDA progressed and was extremely strong one week after the test (+++). The patient also showed positive test reactions to a blend of HDDA and urethane acrylate (+), propoxylated neopentyl glycol diacrylate (++) and nickel sulphate (+). Based on her clinical symptoms and histopathological examinations, both at the site of the allergic lesions and at the site of the positive patch test to HDDA, the woman was diagnosed with toxic epidermal necrolysis (TEN) due to exposure to UV-cured inks. TEN is characterised by widespread erythema, necrosis, blisters and skin detachment on more than 30 % of the body surface, leaving the body susceptible to severe infection. It is characterised by widespread erythema, necrosis, blisters and skin detachment on more than 30 % of the body surface, leaving the body susceptible to severe infection. It is s very severe but rare skin disorder that may even be life threatening.

- A 50-year old man who was exposed to two acrylic products in his work in the printing industry developed what was described by the authors as very severe bullous allergic contact dermatitis after three years at the work-place (Vogel & Schuttelaar, 2013, Vogel, Christoffers et al. 2014). The products contained 93 % HDDA and 97 % glycidyl methacrylate (GMA) respectively. The reactions started with mild eczema on the knee, fingers and wrists that developed into tense blisters within 24 hours. The lesions healed without scar formation within 10 days. The man showed strong positive patch test reactions (+++) to HDDA and GMA and also to a number of other acrylates that had not been identified as components of the glue. Since HDDA and GMA accounts for the major exposures and gave a strong patch test response, the authors identify these substances as the most likely cause of the reaction. According to the authors, the positive patch tests to other acrylates are likely attributed to cross-reactivity or concomitant sensitisation to acrylates not stated in the MSDS.

- A 50-year old man working in the printing industry developed a severe allergic skin reaction after a work place accident were he spilled a bucket of effluent from the printing process over himself (Morgan and Fewings 2000). The authors described the condition as severe allergic contact dermatitis. The allergic reaction appeared ten days after the accident, when the man put on the same trousers as he had worn at the time of the accident. Within a couple of hours, he got a burning sensation that later developed into severe dermatitis at the buttocks. HDDA was one of the main acrylates used in the factory and patch tests later showed that the patient was sensitised to a number of acrylates including HDDA (++).

- A 51-year old man working in the printing industry developed hand dermatitis from a few weeks after he had started to handle UV-cured acrylates in his work (Morgan and Fewings 2000). The patient underwent showed positive patch test reaction to HDDA (++) and the HDDA primed plastic coated sheet he was exposed (+). He did not show positive patch test to any of the other twenty three acrylates he was tested for. According to the case report, the man kept on being exposed to the priming agent at work and consequently, he continued to suffer from hand dermatitis.

Five cases of beauticians who suffer from allergic contact dermatitis and show positive patch tests to HDDA have been reported in the literature (Cravo, Cardoso et al. 2008, Roche, de la Cuadra et al. 2008, Pesonen, Kuuliala et al. 2012, Kiec-Swierczynska, Krecisz et al. 2013). The exact composition of the acrylic glues are not revealed in these cases and the authors have not tried to identify the most likely cause of the allergic reactions. The described symptoms involve for example eczema, oozing lesions, and blisters of the hands and face and irritation in nose and eyes. It was reported that the patients had to change work tasks or profession and some

of the patients experienced recurring symptoms in their new work as they again were exposed to acrylic compounds.

Equivalent level of concern assessment

In order to identify a substance as a SVHC under Article 57(f) of Regulation (EC) 1907/2006 (REACH) an ELoC assessment must be carried out showing that there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances that fulfil the criteria in REACH Article 57(a-e). The ELoC assessment for HDDA was carried out as described in ECHA's general approach for identification of SVHC under article 57(f) considering the following factors (ECHA 2012):

Type and severity of possible health effects

The ECHA discussion paper describes severe skin damage as follows *"e.g. blistering that can burst. Skin function (integrity) is impaired, possibly leading to infection. Ongoing exposure can lead to chronic inflammation and scar formation. Minimal or a single small focus of scarring does not normally constitute "severe organ damage or major permanent functional change" in the skin as an organ."*

Data from experimental animal studies and studies in humans show that non-cured HDDA is a very potent skin sensitiser that can cause sensitisation manifested as mild to very severe allergic contact dermatitis (Morgan and Fewings 2000, Constandt, Hecke et al. 2005, Kiec-Swierczynska, Krecisz et al. 2005, Goon, Isaksson et al. 2006, Teik-Jin Goon, Bruze et al. 2007, Aalto-Korte, Alanko et al. 2008, Ido, Kiyohara et al. 2012, Christoffers, Coenraads et al. 2013, Ramos, Cabral et al. 2014, Vogel & Schuttelaar, 2013, Vogel, Christoffers et al. 2014). This is supported by case reports of occupational allergic contact dermatitis to HDDA from exposure to acrylic based products, such as printing inks and artificial nail products (see above for more detailed description). The reported cases describe patients that suffer from allergic contact dermatitis of varying severity, involving erythema, bullous and oozing skin lesions and skin detachment. The case reports also show that the patients can develop symptoms after a single or few exposures, thus indicating that HDDA is a potent skin sensitiser in humans. The symptoms are most often located to the exposed areas, usually hands and arms and sometimes the face, but may also spread to other parts of the body. The affected skin has a disrupted barrier function making it more susceptible to other hazardous substances and to microbial infections. Most notable is one patient that developed toxic epidermal necrolysis (TEN), after occupational exposure to printing inks containing HDDA. The patient suffered from severe skin lesions covering more than 30% of the body that required hospital care.

In conclusion, HDDA has the capacity to cause severe skin damage in humans. These effects involve blistering and disrupted skin integrity, as described in the ECHA discussion paper. It can be assumed that prolonged exposures to HDDA may lead to permanent skin damage, such as scarring. It is noted that CMR SVHC substances can cause adverse effects with a broad range of severity.

Irreversibility of health effects

The ECHA discussion paper states: *"In the case of skin sensitisers, the induction phase of sensitisation is irreversible, however the organ dysfunction resulting from elicitation is generally seen to be reversible i.e. the allergic reaction by the skin disappears when exposure to the sensitising agent is eliminated. In some instances, skin sensitisers can induce irreversible lesions (e.g. large lesions on the skin, leaving permanent scars and/or discoloration of the skin). However it is unusual to see irreversible damage at an early stage."* Further, it is stated that *"one could argue that the irreversible sensitisation induction is in fact an adverse effect, as it leads to a disposition of the sensitised individuals."*

It is generally acknowledged that the induction phase of sensitisation is an irreversible effect as the immunological system has been permanently modified. The elicitation phase on the other hand is usually reversible if all exposure stops. Persons experiencing severe allergic

dermatitis may need medical treatment. A sensitised person can no longer be exposed to even low concentrations of the sensitising allergen, or other cross-reacting substances, without the risk of developing a severe allergic skin reaction. Thus, a person who is sensitised to HDDA can only be free from symptoms if he or she can completely avoid exposures to HDDA and other cross-reacting acrylates. In addition, in severe cases, the allergic reaction may lead to permanent skin damage.

Indeed, the case reports on HDDA describe patients experiencing recurring symptoms following repeated exposures. The allergic reactions are of such severity that one may assume that ongoing exposure may lead to permanent skin damage, such as scarring.

A recent judgement by the Court of Justice of the European Union gives support to the conclusion that the adverse health effects from sensitising substances should be considered irreversible[9]. The court ruled that adverse health effects of the respiratory sensitisers hexahydromethylphthalic anhydride (MHHPA) and hexahydrophthalic anhydride (HHPA) may be considered irreversible because the induction phase of an allergy is irreversible and it cannot be ruled out that prolonged exposure to the anhydrides can lead to irreversible effects, namely permanent lung damage. Since the development of allergic skin reactions occurs according to similar principles as allergic lung reactions, i.e. involving an immunological irreversible induction phase followed by an elicitation phase, the skin sensitising effects of HDDA should also be considered irreversible. Also for allergic contact dermatitis it cannot be ruled out that prolonged skin exposure may lead to permanent skin lesions such as scaring.

In conclusion, the skin sensitising (initiation) effect of HDDA is irreversible whereas the allergic skin reaction at elicitation are in general reversible provided that the exposures stop. However, prolonged exposures to HDDA may cause irreversible skin damage, such as scarring.

Delay of health effects

In cases where the relationship between exposure and health effect is abstruse, for example because of a substantial delay between exposure and effect, the level of concern about the substance may be elevated (Basketter and Kimber 2014). The health effects of skin sensitisers can be delayed in two ways. First, sensitisation is not always immediate. It usually requires repeated exposures and may take week to years to develop. Second, because the actual sensitisation is asymptomatic, the affected individuals do not know that they have become sensitised until an allergic reaction is elicited. Reports show that it in some cases may take years from the initial exposures to HDDA until the patient develop allergic contact dermatitis, making it difficult for workers to take precautionary actions in time to avoid development of sensitisation (Morgan and Fewings 2000, Ido, Kiyohara et al. 2012, Vogel, Christoffers et al. 2014).

In conclusion, as for CMR substances there may be long/medium delays between the start of the induction phase to HDDA and appearance of clinical symptoms.

Derivation of a safe level of exposure

The ECHA discussion paper states that *"in the context of the 'equivalent level of concern' debate it is felt that an inability to derive a safe concentration may warrant a higher 'level of concern' being associated with the substance in question."*

Skin sensitisation is in principle regarded as a threshold effect, although in practice it may be very difficult to determine a safe level for human exposure (ECHA 2013). Currently there are no available dose-response data from studies in animals or humans that support determination of a quantitative DNEL for HDDA, as is also concluded in the REACH registration dossier. This means that all exposures to HDDA may increase the risk for sensitisation and that a safe condition of use may be difficult to establish.

Quality of life

The ECHA discussion paper states that *"serious impairment of a person's quality of life does*

[9] JUDGMENT OF THE GENERAL COURT (Fifth Chamber), Case T-135/13, 30 April 2015

not play a role in identifying a substance as an SVHC, however in the context of the 'equivalent level of concern' debate it is felt that such impairment warrants a higher 'level of concern' being associated with the substance in question." It is further stated that *"In the case of both respiratory sensitisers and skin sensitisers, once a person is sensitised to an allergen in the workplace (e.g. hairdressers who become sensitised to hair dye ingredients), the person's exposure to that substance needs to be eliminated. In most cases, this means that the person cannot work in their chosen profession any more. Re-training may then be needed, which can lead to a significant impact on that person's quality of life."*

The overall data show that HDDA can cause occupational contact dermatitis, a condition recognized to have an impaired quality of life that can be directly related to the physical symptoms and also to anxiety caused by technical and social difficulties at work and the risk of losing their jobs (Skoet, Zachariae et al. 2003, Benyamini, Goner-Shilo et al. 2012, Boehm, Schmid-Ott et al. 2012). The affected persons must be removed from all exposures to HDDA, cross-reacting acrylates, which means that retraining may be needed, and they may not be able to work in their chosen profession. In addition, cross-reactivity between HDDA and other acrylates aggravates this problem further as it may be more difficult to find a new suitable job or avoid exposure in everyday life. several case reports of occupational allergic contact dermatitis caused by HDDA describe patients who experience difficulties at work that are associated with a negative impact on quality on life.

Societal concern:

The ECHA discussion paper states that *"Societal concern does not play a role in identifying a substance as an SVHC, however in the context of the 'equivalent level of concern' debate it is felt that significant societal concern may warrant a higher 'level of concern' being associated with the substance in question."*

The overall data show that HDDA can cause occupational contact dermatitis, which is recognized as a common condition with a heavy socioeconomic impact involving large costs related to a reduced productivity at work, retraining of the affected individuals, sick leave and health care (Diepgen, Scheidt et al. 2013, Saetterstrom, Olsen et al. 2014). However, there are no reliable data describing how common occupational contact dermatitis to HDDA is in the EU or to acrylates in general. It is therefore not possible to do accurately estimate the societal costs from contact allergy to HDDA. In addition, the increasing use of HDDA, both in terms of volumes and products on the EU market, indicate that the problems will increase in the future if no regulatory actions are taken to minimise the risks.

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