OPINION OF THE MEMBER STATE COMMITTEE

ON THE IDENTIFICATION

OF HEXAMETHYLENE DIACRYLATE (HEXANE-1,6-DIOL DIACRYLATE)

AS A SUBSTANCE OF VERY HIGH CONCERN

According to Articles 57 and 59 of
Regulation (EC) 1907/2006[1]

Adopted on 10 December 2015

This opinion concerns

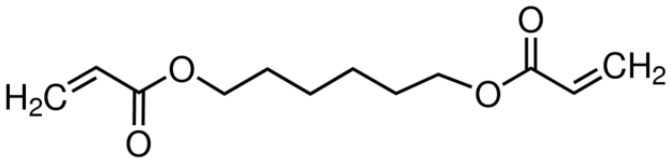
Substance name: Hexamethylene diacrylate (hexane-1,6-diol diacrylate) (HDDA)

EC number: 235-921-9

CAS number: 13048-33-4

Molecular formula: $C_{12}H_{18}O_4$

Structural formulas:



[1]Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

Sweden presented a proposal in accordance with Article 59(3) and Annex XV of the REACH Regulation (24 August 2015, submission number EC018749-46) on identification of *hexamethylene diacrylate (hexane-1,6-diol diacrylate) (HDDA)* as a substance of very high concern due to its skin sensitising properties.

The Annex XV dossier was circulated to Member States on 31 August 2015 and the Annex XV report was made available to interested parties on the ECHA website on the same day according to Articles 59(3) and 59(4).

Comments were received from both Member States and interested parties on the proposal.

The dossier was referred to the Member State Committee on 17 November 2015 and was discussed in the meeting on 7-11 December 2015 of the Member State Committee.

MSC **did not reach** unanimous agreement on whether the information provided in the SVHC proposal is sufficient to constitute an equivalent level of concern to CMRs in accordance with Article 57 (f) of the REACH Regulation.

Pursuant to Articles 59 (9) and 85(8) of REACH in order for the Commission to draft a proposal on the identification of the substance in accordance with the procedure outlined in Article 133 (3) of the REACH Regulation, the Member State Committee provides this opinion, consisting of the view of the majority of its members, including its grounds.

Nine MSC members expressed a minority view, including their grounds, that is made available in a separate document.

In accordance with Article 59 (9), a final decision on the identification of HDDA shall be taken in accordance with the procedure referred to in Article 133(3).

Opinion of the Member State Committee in accordance with Article 59(8):

Hexamethylene diacrylate (hexane-1,6-diol diacrylate) **should be identified as a substance meeting the criteria of Article 57 (f) of REACH because it is a substance with skin sensitising properties for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those for other substances listed in paragraphs (a) to (e) of Article 57 of REACH.**

UNDERLYING ARGUMENTATION
FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN

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 Sens. 1.

Data from studies in animals (Guinea pig maximization tests) show that HDDA is 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 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 conditions involve 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 characterized 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 sensitized 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 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 23 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 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 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 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 (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[2]. 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

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

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 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 safe conditions 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 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.

Conclusion:

Taking into account all available information on the intrinsic properties of HDDA and its adverse effects, it is concluded that this substance should be regarded as a substance for which there is scientific evidence of probable serious effects to humans which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.

Reference:

Support Document to the MSC opinion on *Hexamethylene diacrylate (hexane-1,6-diol diacrylate)* (Member State Committee, 10 December 2015)