Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate; isobornyl acrylate

EC Number: 227-561-6
CAS Number: 5888-33-5

CLH-O-0000006803-72-01/F

Adopted

11 June 2020

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CLH-O-0000006803-72-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: ***exo*-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate; isobornyl acrylate**

EC Number: **227-561-6**

CAS Number: **5888-33-5**

The proposal was submitted by **Germany** and received by RAC on **3 June 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **24 July 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **24 September 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **11 June 2020** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	*exo*-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate; isobornyl acrylate	227-561-6	5888-33-5	Skin Sens. 1	H317	GHS07 Wng	H317			
RAC opinion	TBD	*exo*-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate; isobornyl acrylate	227-561-6	5888-33-5	Skin Sens. 1A	H317	GHS07 Wng	H317			
Resulting Annex VI entry if agreed by COM	TBD	*exo*-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate; isobornyl acrylate	227-561-6	5888-33-5	Skin Sens. 1A	H317	GHS07 Wng	H317			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Isobornyl acrylate is an acrylic monomer used in plastic materials for the manufacture of various products, including medical devices for diabetes patients.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) has provided the results of one *in vivo* Local Lymph Node Assay (LLNA) with isobornyl acrylate in mice and clinical case observations in humans having dermal exposure to isobornyl acrylate.

Animal studies

In the LLNA (RCC, 2012), performed under GLP conditions and according to OECD TG 429, the potential of the substance to cause skin sensitisation was investigated using isobornyl acrylate at concentrations of 5, 10 and 25% (w/w), and the vehicle was acetone:olive oil in the proportion of 4:1 (v/v). The positive control group, using α-hexyl cinnamic aldehyde, was included in the study for validation purposes.

At the time of preparing CLH report, the DS had no access to the full study report but noted, based on the information in the REACH registration dossier, that the expiration date of the test substance batch used in this study had been exceeded by more than five years, therefore rated the study as "not reliable" (Klimisch score 3). During the CLH consultation, the registrant informed that the expiration date of the tested batch was in fact a typing error in the REACH registration dossier. The DS, having analysed the full study report, concluded the same and upgraded the study reliability to Klimisch score 1. Consequently, the DS proposed to use the LLNA (RCC, 2012) as a key study in support of the proposed classification.

In the LLNA induction phase, using isobornyl acrylate at concentrations of 5, 10 and 25% (w/w), a vehicle or α-hexyl cinnamic aldehyde was applied to the dorsal surface of each ear (25 µL per ear) for 3 consecutive days. Five females (nulliparous and non-pregnant) were used, in each of three dose groups and in 1 vehicle group (20 animals in total). Five days after the first topical application, the proliferation of lymphocytes in the lymph node (2 nodes per animal) draining the application site was measured based on incorporation of 3H-methyl thymidine (day 6).

No mortality, systemic toxicity or local skin irritation were observed during the study. The obtained individual DPM values minus background ^{3}HTdR level were used to calculate Stimulation Indices (SI) for each treatment group. The positive result obtained with α-hexyl cinnamic aldehyde validated the test system used. The results are shown in the table below:

Treatment	Concentration (%)	Stimulation Index (SI)
Vehicle control (acetone/olive oil (4:1 v/v)	0	1.0
Isobornyl acrylate	5	4.07
Isobornyl acrylate	10	14.07
Isobornyl acrylate	25	22.84

A significant lymphoproliferation (SI > 3) was obtained at isobornyl acrylate concentrations of 5, 10 and 25%, with a clear dose-response relationship. However, the EC3 value (i.e. the amount of chemical that is required to induce an SI of 3) could not be calculated because no lower concentrations were tested.

Human data

The DS presented the results of several case-reports and clinical studies showing that, in some diabetes patients wearing the glucose monitoring sensors or insulin pumps from 14 days up to 18 months, an allergic contact reaction to the adhesive glue, used to fix the sensor to the skin, developed. In a study of Herman *et al.* (2017), 12 out of 13 patients with allergic contact dermatitis caused by a flash glucose monitoring system had positive reactions in the skin patch test with 0.1-0.01% solution of isobornyl acrylate, showing skin sensitisation to this substance. In two patients using continuous glucose monitoring systems, skin reactions developed underneath the sensor. The patch tests demonstrated that both persons had acquired skin sensitisation to isobornyl acrylate (Corazza *et al.*, 2018; Oppel *et al.*, 2018).

Observation of 120 patients using a sensor-based glucose monitoring system fixed to the skin with medical-grade adhesive containing isobornyl acrylate (exact composition of the glue unknown) indicated that adverse skin reactions potentially attributed to skin sensitisation had developed in 10 patients, thus in approximately 8% of sensor users (Bolinder *et al.*, 2016, Aerts *et al.*, 2017; Bolinder *et al.*, 2017). Since no patch tests with isobornyl acrylate were done in these patients, it cannot be ruled out that these reactions could be caused by other glue constituents (Aerts *et al.*, 2017; Bolinder *et al.*, 2016; Bolinder *et al.*, 2017).

In 4 cases of contact dermatitis caused by the insulin pump, the patch tests with isobornyl acrylate confirmed the allergic aetiology of the skin reaction, indicating that the patients had a skin sensitisation to this substance (Raison-Peyron *et al.*, 2018)

In two diabetes mellitus patients with eczema in the place of skin contact with insulin pump the skin patch tests revealed that they were sensitised to isobornyl acrylate being one of the glue ingredients used in both cases (Busschots *et al.*, 1995)

In a 47 year-old worker with therapy-resistant hand eczema, the skin symptoms cleared during holidays and worsened after returning to work. During work, he had a dermal contact with glass fibres with coatings containing isobornyl acrylate. The patch test disclosed strong skin sensitisation to isobornyl acrylate (Christoffers *et al.*, 2013).

On the other hand, no skin sensitisation to isobornyl acrylate were detected with patch tests in 81 workers manufacturing electric coils for television displays, which *inter alia* worked for four years using glue containing 25-50% of isobornyl acrylate (Kieć-Świerczyńska *et al.,* 2005). It is noted that the magnitude of dermal exposure to isobornyl acrylate of these workers could be very small in terms of amount contaminating skin and in daily duration, since application and curation of the glue were done automatically.

Based on the data presented above, the DS proposed to classify isobornyl acrylate as a skin sensitiser 1 (Skin Sens. 1; H317: May cause an allergic reaction) without sub-categorisation. No Specific Concentration Limit was proposed.

Comments received during public consultation

Two MSCAs and one company-manufacturer supported classification of isobornyl acrylate as Skin Sens. 1; H317: May cause an allergic reaction.

One company-manufacturer noted that in the CLH dossier, the DS assessed the LLNA provided in the REACH registration dossier as key study as invalid due to the observation that the test material was expired at the time of testing. The company has checked the information given in the IUCLID data base and found that there is a typing error not recognized earlier. The registrant corrected this error and provided the DS with the detailed information indicating the integrity of the test substance. The company indicated that the LLNA used as key study is valid, but the results do not allow a differentiation between Skin Sens. 1A or 1B. In their response the DS acknowledged this clarification allowing to upgrade the study reliability to Klimisch score 1, and thus considered this as the key study in support of the proposed classification. With respect to the potential sub-categorization, the possibility of obtaining an extrapolated EC3 was indicated by one MSCA and the DS recommended that RAC should indeed consider this possibility.

Assessment and comparison with the classification criteria

Animal data

The LLNA (RCC, 2012) was performed in GLP conditions and according to OECD TG 429 (EU Method B.42). The batch of isobornyl acrylate used in this study had a purity of 99.57% and it was used before the end of expiration date.

In the range finding test, it was found that application of isobornyl acrylate on the dorsal surface of both ears at concentration of 50 and 100% caused erythema and increase in ears thickness and weights well above the respective historical vehicle values. At a concentration of 25%, very slight erythema was observed, but no significant increase in ears thickness or weights. No erythema was observed at after application of isobornyl acrylate at concentration of 10%. Based on the results of range finding, the LLNA was performed using concentrations of 5, 10, and 25% (w/w).

The periodic positive control experiment was performed within 2 months before the start of main study with α-hexyl cinnamic aldehyde in acetone:olive oil 4:1 (v/v) using the same strain of mice. The SI equal 3.73 for α-hexyl cinnamic aldehyde applied at concentration of 25% was at the lower range of SI values obtained in this laboratory within 2011-2012 in 10 positive control experiments for α-hexyl cinnamic aldehyde applied at concentration of 25% (3.37 - 10.77). No deviations from the study plan were reported and the study is considered as reliable with Klimisch score 1.

In the main study isobornyl acrylate at concentrations 5, 10 and 25% has produced SI values of 4.07, 14.07 and 22.84, respectively. Concentrations below 2% were not tested, therefore there are no experimental data providing direct evidence that isobornyl acrylate at concentration at or below 2% is capable to induce an SI of 3, although such a possibility seems to be probable. The study authors concluded that the EC3 value could not be calculated, since all obtained SI´s were above the threshold value of 3, and linear interpolation was not possible.

During the consultation, one MSCA suggested that it would be helpful to have an extrapolated EC3 value for skin sensitising potency assessment and, in their response, the DS asked RAC to

consider this possibility. The EC3 in LLNA is usually determined by linear interpolation using two SI data points, one immediately below and one immediately above the concentration at which a tested substance is producing SI value of ≥ 3 (Basketter *et al.*, 1999). With regards to extrapolation of EC3 values, in cases where interpolation is not possible, a few different methods can be used (see below). However, there is no internationally accepted method for EC3 extrapolation when the experimentally determined SI values are all above 3. This is further examined using different extrapolation techniques under 'In-depth analysis by RAC' in the Background Document.

The extrapolation of EC3 values based on the available data demonstrate that these values are different depending upon the mathematical model used. Noting this variation in sensitising potency depending upon the method of extrapolation used, RAC considers that EC3 values extrapolated with linear regression, quadratic regression and log linear extrapolation are not equivalent to a value obtained in the experiment, therefore these values do not constitute sufficient evidence for subcategorization.

When the data warrant classification as Skin Sens. 1, but do not enable subcategorization, RAC follows recommendations in the Guidance on the Application of the CLP Criteria (version 5.0 July 2017, CLP Guidance): "*although the criteria in the table 3.4.4 for classification to subcategory 1B are fulfilled, the classification for subcategory 1A may not be excluded and therefore the substance should be classified as a Category 1 skin sensitiser*". It is noted that REACH information requirements (as amended by Commission Regulation (EU) 2016/1688) for skin sensitisation includes a requirement for a potency assessment, i.e. an assessment of whether a substance "*can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A)*". However, there is an exception to this requirement if there is existing animal information available, i.e. a study, which was initiated or conducted before 11 October 2016, such as the RCC study (2012), that does not allow an assessment of potency and thus only a conclusion in category 1 is possible. In such cases, no further testing to assess potency is required under REACH. Therefore, based on existing animal data, isobornyl acrylate warrants classification as Skin Sens. 1; H317: May cause an allergic skin reaction.

Human data

The existing data clearly demonstrate, based on positive patch tests, that isobornyl acrylate is a skin sensitiser in humans (Busschots *et al.,* 1995; Christoffers *et al*., 2013; Herman *et al.* 2017; Corazza *et al.,* 2018; Oppel *et al.,* 2018; Raison-Peyron *et al.,* 2018) or is strongly suspected to be skin sensitiser in humans, although the casual link was not confirmed, since patch testing was not done (Aerts *et al.,* 2017; Bolinder *et al.,* 2016; Bolinder *et al.* 2017).

The positive data comes mostly from the investigations of diabetes patients using the sensors for continuous monitoring of glucose in blood or insulin pumps made from plastic materials containing isobornyl acrylate and attached to human skin with glue also containing isobornyl acrylate (Busschots *et al.,* 1995; Herman *et al.*, 2017; Corazza *et al.*, 2018; Oppel *et al.*, 2018; Raison-Peyron *et al.*, 2018). Only one case of skin sensitisation to isobornyl acrylate was due to occupational exposure (Christoffers *et al.*, 2013). No cases of occupational allergic contact dermatitis were noted in 81 workers involved in the manufacture of electric coils for television displays and exposed to glue containing several acrylates including isobornyl acrylate, although 9 of workers had allergic contact dermatitis with positive patch tests with other acrylates. The process of glue application and curing was automatic, but after that, the workers examined the coils for defects and manually disassembled the defective ones. To ensure better operative precision, they used vinyl protective gloves with severed fingertips. No information on the levels of exposure was provided (Kieć-Świerczyńska *et al*., 2005).

The studies on sensitised diabetes patients provide evidence that the exposure level to induce sensitisation might be quite low. In the study of Herman *et al.* (2017), isobornyl acrylate was detected in acetone extracts of adhesive patches of various plastic parts of whole 'FreeStyle Libre' glucose sensors used by 11 sensitised persons. The extract made from the adhesive patches contained isobornyl acrylate at concentration of 0.006%, corresponding to 2 - 50 µg/patch, thus to a surface dose of 0.2 - 5 µg/cm^2 of adhesive patch. In other parts of the glucose sensors, concentrations of isobornyl acrylate were in the range of 0.003% to 0.4%.

In the case study of Oppel *et al.* (2018), isobornyl acrylate was detected in methanol eluate of the 'OmniPod' insulin pump used by a young patient sensitised to isobornyl acrylate. The concentration of isobornyl acrylate in eluate from the skin contact side of the OmniPod insulin pump amounted to 10 µg/10 mL (0.0001%). Taking into account the immersed surface area of an insulin pump this corresponds to a dose/area of ca. 0.53 µg/ cm^2. Before using insulin pump, the patient was using Freestyle Libre glucose sensor, what could have led to an induction exposure, while that caused by the pump was an elicitation exposure.

Raison-Peyron *et al.* (2018) found that, in the OmniPod insulin pumps used by 4 persons which became sensitised to isobornyl acrylate, the concentrations of this substance corresponded to ca. 5 µg in the used unit and to 40 -190 µg in the unused units. The adhesive patches contained ~ 5 µg of isobornyl acrylate per the patch.

The results of these studies indicate that dermal exposure needed for induction of skin sensitisation to isobornyl acrylate may be low, in a range of several µg/cm^2, while the time of daily exposure was 24 h/day, and the duration of exposure was from two weeks to 18 months (Herman *et al.*, 2017). The level of exposure in these studies is not determined so precisely as in Human Repeat Insult Patch Tests (HRIPT), which however cannot be requested for the purposes of the CLP Regulation.

The existing exposure data (Herman *et al.*, 2017; Oppel *et al.*, 2018; Raison-Peyron *et al.*, 2018) strongly suggest that the threshold dose of isobornyl acrylate to induce sensitisation in diabetes patients is below 500 µg/cm^2, therefore it is highly probable that it fulfils the HRIPT classification criterion for the Skin Sens. for 1A (CLP Regulation, Annex I, 3.4.2.2.2.1).

Noting that the induction exposure is low, a weight of evidence approach is applied to evaluate whether the existing human data on sensitising properties of isobornyl acrylate fulfils the criteria (CLH Regulation, Annex I, 3.4.2.2.2.1) of human evidence for sub-category 1A:

(a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT — induction threshold);

(b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;

(c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

In the weight of evidence in line with the requirement set in CLP Regulation *3.4.2.2.4.1: evidence shall include any or all of the following using a weight of evidence approach:*

(a) positive data from patch testing, normally obtained in more than one dermatology clinic;

(b) epidemiological studies showing allergic contact dermatitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;

(c) positive data from appropriate animal studies;

(d) positive data from experimental studies in man;

(e) well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic;

(f) severity of reaction may also be considered.

As described above, there are positive data from patch testing obtained in more than one dermatology clinic indicating that isobornyl acrylate is a human skin sensitiser at rather low exposure levels. The incidence of skin sensitization among diabetes patients exposed to isobornyl acrylate through contact with glucose sensors or insulin pumps containing that substance is relatively high. Among 15 subjects suffering from severe allergic contact dermatitis caused by 'FreeStyle Libre' glucose sensors, isobornyl acrylate was confirmed by patch tests as a relevant and causative contact allergen in the majority of them (Herman *et al*., 2017). In Finland, 63 patients out of 6567 (1.0%) of 'FreeStyle Libre' sensor glucose users developed cutaneous adverse reactions, and 51 patients (81%) of them shown to be sensitized to isobornyl acrylate, equalling a 0.8% prevalence of sensitization in the whole population of 'FreeStyle Libre' users (Aerts *et al.*, 2020). Finnish authors stipulated that 1% of patients experiencing skin problems are actually referred patients, mostly experiencing severe dermatitis, whereas the real number of patients experiencing "any" type of skin adverse effect is probably much higher, that is, in the magnitude of 5.0% of the exposed population. According to the French governmental agency ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), the number of cutaneous adverse events arising from the particular glucose sensor FreeStyle Libre containing isobornyl acrylate has been stable since June 2018 with approximately 0.2% of patients requiring a medical follow-up (Aerts *et al.*, 2020).

In line with the recommendations given in Table 3.3 of the CLP Guidance on relatively high or low exposure, it is concluded that the level of human exposure to isobornyl acrylate required to induce skin sensitisation is low.

In line with the recommendations given in Table 3.4 of the CLP Guidance, sub-categorisation decision table, it is established that relatively high frequency of occurrence of skin sensitisation (≥ 0.2%) to isobornyl acrylate is shown among diabetes patients exposed to this substance, forcing these patients to seek medical advice, thus classification to Sub-category 1A is justified.

Since the available human data indicate that the substance at relatively low level of exposure causes a relatively high incidence of skin sensitisation among exposed people, RAC is of the opinion that isobornyl acrylate warrants **classification as Skin Sens. 1A; H317: May cause an allergic skin reaction.** No specific concentration limit is proposed.

Additional references

Aerts O. *et al.* (2020) Isobornyl Acrylate. Dermatitis, 2020, 31 (2): 4–12

Gould J.C. & Taylor S. (2011). Hazard identification of strong dermal sensitizers. Toxicology Mechanisms and Methods, 2011; 21(2): 86–92

Basketter D.A. *et al.* (1999) A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. Journal of Applied Toxicology, 1999, 19:261-266

Ryan C.A. *et al.* (2007) Extrapolating local lymph node assay EC3 values to estimate relative sensitizing potency. Cutaneous and Ocular Toxicology, 2007, 26: 135–145.

ANNEXES

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).