Committee for Risk Assessment

RAC

Annex 1

Background document

to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

11 June 2020

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

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

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

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

Index Number: **-**

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ANNEX 1 – BACKGROUND DOCUMENT TO RAC OPINION ON EXO-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL ACRYLATE; ISOBORNYL ACRYLATE

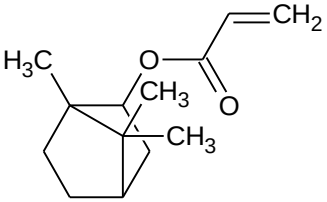
CONTENTS

ANNEX 1 – BACKGROUND DOCUMENT TO RAC OPINION ON EXO-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL ACRYLATE; ISOBORNYL ACRYLATE

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl prop-2-enoate
Other names (usual name, trade name, abbreviation)	isobornyl acrylate 2-Propenoic acid, (1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester, rel- (CAS name) 2-Propenoic acid, 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester, exo- (other name)
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	227-561-6
EC name (if available and appropriate)	exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate
CAS number (if available)	5888-33-5
Other identity code (if available)	
Molecular formula	$C_{13}H_{20}O_2$
Structural formula	
SMILES notation (if available)	C=CC(=O)OC1CC2CCC1(C)C2(C)C
Molecular weight or molecular weight range	208.30 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	Not applicable

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)[1]**
exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate EC No. 227-561-6 CAS No. 5888-33-5	100%	-	Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1B STOT SE 3; H335 Aquatic Acute 1 Aquatic Chronic 1

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Not applicable				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
Not applicable					

[1] according to REACH registration dossiers notifications

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Current, proposed, and resulting harmonised classification and labelling for isobornyl acrylate

	Index No	International Chemical Identification	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	-										
Dossier submitter's proposal	TBA	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	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	TBA	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	-	-	-

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Not evaluated in this dossier	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route		
Acute toxicity via dermal route		
Acute toxicity via inhalation route		
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation	No data identified	No
Skin sensitisation	Skin Sens. 1	Yes
Germ cell mutagenicity	Not evaluated in this dossier	No
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment		
Hazardous to the ozone layer		

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

To date there is no harmonised classification and labelling available for isobornyl acrylate (IBOA).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

As of April 2019, the C&L Inventory currently contains 171 notifications for IBOA with respect to skin sensitisation:

- Skin Sens 1 (43 notifications);
- Skin Sens 1A (1 notification).
- Skin Sens 1B (127 notifications);

More importantly, a further 458 notifications do not classify IBOA for skin sensitisation at all.

Differences in self-classification between different notifiers in the C&L Inventory and/or between different registration dossiers have been discovered. The dossier submitter disagrees with the current self-classification by the notifiers and/or registrants. Furthermore, medical devices containing IBOA are sold and used on the European market and were linked to a number of cases of skin contact dermatitis. Therefore, action at community level is needed to protect exposed individuals from the risk of being sensitised to IBOA.

5 IDENTIFIED USES

IBOA is an acrylic monomer that polymerises when exposed to sources of free radicals (Bolinder et al., 2016; Foti et al., 2016). It is used in plastic materials, also for valves, tubes lining, stoppers, sealants, coatings and inks (Foti et al., 2016) but also in the plastic materials used for the production of medical devices for diabetes patients (Oppel et al., 2018; Raison-Peyron et al., 2018). Furthermore, paint (Christoffers et al., 2013) and glues might contain acrylates (Aalto-Korte et al., 2008; Kiec-Swierczynska et al., 2005).

5.1 Workers

IBOA has wide-spread uses. It is used in formulation or re-packing, at industrial sites and in manufacturing, by workers and professionals. IBOA is used for the manufacture of rubber products and plastic, in paints, coatings and adhesives. It is used in the printing and recorded media reproduction; for the manufacture of plastic products such as for thermoplastic manufacture, as processing aid and in the production of articles[2].

5.2 Consumers

IBOA is used in glucose monitoring sensors worn by diabetic patients. Such sensors consist of a fibre which penetrates the skin and which is attached to a pad glued to the skin with an adhesive which may contain IBOA. The sensors are worn continuously for several (apparently up to 14) days (Aerts et al., 2017; Bolinder et al., 2016; Brahimi et al., 2017; Corazza et al., 2018). It has been reported that lately there is a tendency towards extending the glucose sensor wearing time of glucose monitoring sensors. While it is expected that this will give less rise to injuries of the skin, less trouble with sensor change and lower sensor costs per day, the increased numbers of patients showing skin reactions, in particular allergic contact dermatitis, will be a disadvantage (Heinemann and Kamann, 2016).

Recent publications identified IBOA in insulin patch pumps. Such pumps consist of a "pod" that contains the insulin reservoir and cannula, which can be worn on the skin (for up to 3 days). A so-called "Personal Diabetes Manager" acts as a distant remote control to calculate the exact dose of insulin needed (Raison-Peyron et al., 2018). IBOA was detected in various parts of the unit (Oppel et al., 2018; Raison-Peyron et al., 2018).

Beyond this, ECHA has no public registered data indicating whether or in which chemical products the substance might be used or into which articles the substance might have been processed[2]. However, given the wide-spread use of IBOA, it seems likely that it is also used in consumer products. IBOA might also be a contaminant or impurity in industrial and cosmetic products (wetting agents, surfactants and emulsifiers) that might not be mentioned in material safety data sheets (Foti et al., 2016).

[2] https://echa.europa.eu/substance-information/-/substanceinfo/100.025.055 (last accessed 2018-06-11)

6 DATA SOURCES

The data for IBOA were obtained from the REACH Registration Dossier (as of 2018-04-18) as well as from a systematic literature research, which was performed during December 2017 and updated in August 2018 in bibliographical databases such as PubMed[3], SCOPUS[4], Web of Science[5], Embase[6], Toxnet[7], or ScienceDirect[8].

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Physical state at 20°C and 101,3 kPa	Colourless liquid with an ester-like odour	REACH registration dossier	-
Melting/freezing point	< - 20 °C	(Anonymous, 2012)	In analogy to the structural analogue isobornyl methacrylate and including published data, a melting point < - 20 °C can be estimated.
Boiling point	275 °C (1013 hPa)	(Anonymous, 1996)	Measured
Relative density	0.990 g/cm³ (20 °C)	(Evonik Röhm, 2008)	According to DIN 51757; oscillating densitometer
Vapour pressure	0.013 hPa at 20 °C 0.021 hPa at 25 °C	(Siemens, 2012)	OECD 104; dynamic method
Surface tension			Based on structure, surface activity is not expected.
Water solubility	19.8 mg/L at 20 °C, pH 6.06	(Noack, 2012)	OECD 105, flask method
Partition coefficient n-octanol/water	Log P_{ow}: 4.52 at 20°C	(Evonik Röhm GmbH, 2008)	OECD 117; HPLC method
Flash point	-	-	-
Flammability	-	-	-
Explosive properties	-	-	-
Self-ignition temperature	-	-	-
Oxidising properties	-	-	-
Granulometry	-	-	-
Stability in organic solvents and identity of relevant degradation products	-	-	-
Dissociation constant	-	-	The substance does not contain any ionic, dissociable structures.

[3] https://www.ncbi.nlm.nih.gov/pubmed/
[4] https://www.scopus.com
[5] http://apps.webofknowledge.com
[6] https://www.embase.com
[7] https://www.toxnet.nlm.nih.gov
[8] https://www.sciencedirect.com

Property	Value	Reference	Comment (e.g. measured or estimated)
Viscosity	7.5 - 9.5 cPs at 25 °C	(Anonymous, 1996)	Measured

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this dossier. Proof of sensitisation after dermal contact indicates that enough IBOA is taken up via the dermal route to induce a positive reaction in the skin.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity

10.1.1 Acute toxicity - oral route

Not evaluated in this dossier

10.1.2 Acute toxicity - dermal route

Not evaluated in this dossier

10.1.3 Acute toxicity - inhalation route

Not evaluated in this dossier

10.2 Skin corrosion/irritation

Not evaluated in this dossier

10.3 Serious eye damage/eye irritation

Not evaluated in this dossier

10.4 Respiratory sensitisation

The DS did not identify studies investigating sensitising properties of IBOA in the respiratory tract.

10.5 Skin sensitisation

10.5.1 Animal data

The DS identified one local lymph node assay (LLNA) report (OECD 429, GLP) which shows that exposure to IBOA might cause skin sensitisation *in vivo* (see Table 8).

Table 8: Summary table of animal studies on skin sensitisation

Method, guideline, deviations	**Species, strain, sex, no/group**	**Test substance, positive control**	**Dose levels**	**Results**	**Reference**
LLNA (OECD 429, GLP) Reliability: 3 (not reliable) test substance batch had expired.	Mouse CBA/CaOlaHsd Females 5 animals /group	isobornyl acrylate (IBOA) Positive control: Hexyl cinnamic aldehyde (CAS No 101-86-0)	5, 10, and 25% (w/w) in acetone:olive oil (4+1 v/v)	***Positive*** Stimulation Indices (S.I.) of 4.07, 14.07, and 22.84 were determined with IBOA at concentrations of 5, 10, and 25% (w/w) in acetone:olive oil (4+1 v/v). A clear dose response was observed. An EC_3 value was not calculated.	(RCC, 2012) This study is included in the REACH registration dossier for the substance.

In this LLNA, IBOA dissolved in acetone:olive oil (4+1 v/v) was assessed in concentrations of 5, 10, and 25% (w/w). No systemic toxicity or local skin irritation were observed during the study. No mortality was reported. S.I. of 4.07, 14.07, and 22.84 were determined for the three IBOA concentrations, respectively. A clear dose response was observed. S.I. values of all treatment groups were above the threshold value of 3 and therefore IBOA was found to be a skin sensitiser in the LLNA. The study is not suitable for classification since the test substance batch used had expired at the time of testing and thus it is unclear whether IBOA or possible degradation products thereof had been tested. For a more detailed summary, cf. Annex 1.

10.5.2 Human data

Reportedly, IBOA has caused sensitisation in diabetes patients who used flash or continuous glucose monitoring systems on a daily and continuous basis (Bolinder et al., 2017; Corazza et al., 2018; Herman et al., 2017) as well as insulin patch pumps (Oppel et al., 2018; Raison-Peyron et al., 2018). Children or adolescents might be affected in particular (Heinemann and Kamann, 2016). The available studies are summarised in Table 9 below. Only studies in patients with known exposure to IBOA are included.

Table 9: Summary table of human data on skin sensitisation (sorted by year of publication).

Type of data/report	**Test substance**	**Relevant information about the study**	**Observations**	**Reference**
Case Reports of patients with contact allergy to components of glue in insulin pump infusion sets, patch-tested for allergic reaction to IBOA Reliability: 2 (reliable with restrictions)	IBOA, 0.1% (case no. 1) and 0.001-0.1% (case no. 2), respectively	Case no. 1: A 27 year-old woman who had insulin-dependent diabetes mellitus (DM) since the age of 8 years. She used an insulin pump for a month, then eczema appeared on the abdomen. Case no. 2: A 26 year-old woman who had insulin-dependent DM for 4 years. She had discontinued using an insulin pump after 14 months, because of eczema and abscesses. The lesions had appeared 4 to 5 months since exposure to the device began. The ingredients of the glue used (mainly acrylates) were obtained from the manufacturer and tested,	**Positive strong reactions to IBOA in patch tests** Patch tests with the glue components in negative control subjects were negative. For details, see Annex 1	(Busschots et al., 1995)

Type of data/report	Test substance	Relevant information about the study	Observations	Reference
		IBOA was present, concentration is unknown.		
Reliability: 2 (reliable with restrictions)	IBOA, 0.1% pet.	Dermatological examinations were performed in 81 workers involved in the manufacture of electric coils for television displays, who had inter alia worked for four years using a glue containing IBOA (25–50%). Some workers developed painful fissures of the skin. 12 people reacted to acrylates, but none to IBOA. Cross-reactions with methacrylates were not observed. Patch tests with a 30-allergen series were performed in all subjects (except for 1 worker with extensive psoriasis vulgaris lesions), according to ICDRG criteria; patches were read at D2 and D4.	**Negative** Not suitable for classification, since exposure to the glue is unclear (glue application and curation were done automatically, therefore the amount of skin contact is unknown). For details, see Annex 1	(Kiec-Swierczynska et al., 2005)

Type of data/report	Test substance	Relevant information about the study	Observations	Reference
Case report Reliability: 2 (reliable with restrictions)	0.1% IBOA pet.	A 47 year-old atopic man had therapy-resistant hand eczema. He had been a process operator in a factory producing glass fibres for over 20 years (painting glass fibres with UV-curable paint, printing the glass fibres, covering them with an acrylate coating, and cleaning the machines). His skin problems cleared during holidays, and relapsed when he returned to work. IBOA was a component of the glass fibre coatings and UV-curable paint.	**Strong positive patch-test reaction on days 3 and 7 following 48 h of occlusive exposure** For details, see Annex 1	(Christoffers et al., 2013)
Multi-centre, non-masked, randomised controlled trial Reliability: 2 (reliable with restrictions)	Medical-grade adhesive containing IBOA (exact composition unknown)	Adult patients with well-controlled type 1 diabetes from 23 European diabetes centres were followed for six months to evaluate mean time in hypoglycaemia in an intervention group (n = 120) using a sensor-based, flash glucose monitoring system and a control group (n = 121) using self-monitored glucose testing. 13 adverse events related to the sensor were reported by ten participants in the intervention group: four allergy events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-site symptom (severe); two erythema (one severe, one mild); and one oedema (moderate).	**Positive in ≤ 10/120**[9] However, since the presence of other allergens in the adhesive is possible, adverse effects cannot be attributed to IBOA with sufficient certainty. Not suitable for classification For details, see Annex 1	(Bolinder et al., 2016) See also the additional information in Annex 1 from (Aerts et al., 2017; Bolinder et al., 2017)
Reliability: 2 (reliable with restrictions)	IBOA, 0.01-0.1% in pet. or acetone	15 patients with allergic contact dermatitis caused by a flash glucose monitoring system were patch-tested IBOA was used for patch-testing (13/15 patients) in various concentrations and vehicles. Patch tests were performed with a baseline series and sometimes with additional series, such as plastics and glues, (meth)acrylates, epoxy resins, and/or isocyanates.	**Positive (12/13)** 12 out of 13 patients patch-tested for IBOA showed a positive reaction For details, see Annex 1	(Herman et al., 2017)

9 Due to lack of information in the original publications, it is unclear how many of the „adverse events“ have to be attributed to allergic reactions.

Type of data/report	Test substance	Relevant information about the study	Observations	Reference
Case Report Reliability: 2 (reliable with restrictions)	0.1% IBOA pet	27-year-old male, who had been suffering from diabetes mellitus type I for 6 years, developed chronic eczema on the upper part of the arm after using a continuous glucose monitoring system that was replaced every 14 days. Readings were performed on day (D) 2, D3 and D4.	**Positive reactions were recorded for adhesive and IBOA** For details, see Annex 1	(Corazza et al., 2018)
Case Report Reliability: 2 (reliable with restrictions)	0.1% IBOA pet	A 10-year-old boy with type 1 diabetes started treatment with a glucose monitoring system (Freestyle Libre). The sensor was attached to the upper arm for 14 days. After a few months the patient complained about an itch underneath his sensor that progressively worsened, and an erythematous and vesicular rash developed. Later when using an insulin patch pump (Omnipod) the patient developed similar skin lesions underneath the patch. Patch tests were performed with the baseline allergen series as well as a plastics and glues series (including several acrylates) and classified according to German Contact Dermatitis Research Group criteria.	**All standard tests gave negative results.** Adhesives used for the medical devices gave negative results. **Patch Test with IBOA 0.1% pet gave a strong (++) reaction on day 3**: not found in adhesive, but in other parts of the devices. The amount of IBOA detected in the Omnipod device corresponded to a dose/area of **~0.53 µg/cm^2** (immersed surface area). For details, see Annex 1	(Oppel et al., 2018)
Case Reports Reliability: 2 (reliable with restrictions)	0.1% IBOA pet	4 cases of allergic contact dermatitis caused by the OmniPod insulin pump are reported. Patch tests with IBOA gave positive reactions in all 4 patients.	**4/4 positive** Chemical analyses identified IBOA in different parts of the device. For details, see Annex 1	(Raison-Peyron et al., 2018)

The DS found several studies that indicate a potential of IBOA to cause sensitisation in humans. In adult diabetes type 1 patients, the medical-grade adhesive present in the fixing part of the glucose monitoring system triggered significant positive skin reactions (Aerts et al., 2017; Bolinder et al., 2016; Bolinder et al., 2017; Corazza et al., 2018). IBOA was confirmed as one of the constituents of the adhesive but not specifically tested in the patients. In another study, a patient was specifically patch tested for 0.1% IBOA which elicited strong reactions (Corazza et al., 2018).

The same effect was observed in further studies. For instance, of 15 cases of allergic contact dermatitis caused by a flash glucose monitoring system 12 out of 13 tested individuals were shown to be sensitised to IBOA (Herman et al., 2017). Furthermore, additional case reports of two adult diabetes type 1 patients (Busschots et al., 1995) and of a worker exposed to IBOA at the workplace (Christoffers et al., 2013; Christoffers et al., 2012) have reported specific patch test-positive reactions to IBOA.Workers using glue containing high amounts of IBOA (e.g. 25-50 %) on a daily basis have been shown not to be sensitised to

IBOA (Kiec-Swierczynska et al., 2005). Two more studies identified sensitisation potential of insulin pumps that contain IBOA (Oppel et al., 2018; Raison-Peyron et al., 2018).

Overall, a specific consumer type might be particularly affected due to the use of IBOA-containing products: diabetes patients using flash or continuous glucose monitoring systems as well as patch insulin pumps.

10.5.3 Short summary and overall relevance of the provided information on skin sensitisation

Both an animal test (LLNA, albeit with reliability issues) and human data show that IBOA has the potential to act as a skin sensitiser.

10.5.4 Comparison with the CLP criteria

In Table 10 below, the available human data is compared with the CLP criteria, as described in the Guidance on the Application of the CLP Criteria Version 5.0 – July 2017 (Table 3.2 Relatively high or low frequency of occurrence of skin sensitisation; Table 3.3 Relatively high or low exposure; Table 3.4 Sub-categorisation decision table (ECHA, 2017)). Only the case reports published by (Busschots et al., 1995; Christoffers et al., 2013; Corazza et al., 2018; Oppel et al., 2018; Raison-Peyron et al., 2018) can be used as basis for classification because positive skin reactions were specifically demonstrated for IBOA in these cases. By contrast, Bolinder and co-workers admittedly demonstrated allergic reactions of diabetes patients to an IBOA-containing glue used to affix the sensor of a glucose monitoring system to their arms. However, they could not demonstrate with sufficient certainty that IBOA was the allergenic agent since only the adhesive as a whole was tested (Aerts et al., 2017; Bolinder et al., 2016; Bolinder et al., 2017).

Table 10: Overview on published cases reporting allergic skin reactions after contact to IBOA and comparison of the results with the criteria given in the CLP guidance to determine the level of frequency and exposure.

Reference	(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)
Number of cases	2	1	12	1	1	4
Subjects	**Patients** with insulin-dependent diabetes mellitus (DM) using insulin pumps (Cliniset, Disetronic, Clini Soft)	**Worker** using glass fibre coatings and UV-cured inks	**Patients** with DM type I using continuous glucose monitoring systems (CGMS), (FreeStyle Libre)	**Patient** with DM type I using CGMS (FreeStyle Libre)	**Patient** with DM type I using CGMS (FreeStyle Libre) and insulin patch pumps (Omnipod)	**Patients** with DM (type I) using insulin patch pumps (Omnipod, all cases) and CGMS (FreeStyle Libre, cases 3 and 4)
FREQUENCY	<< 100 published cases in total (= **low frequency**)					
Concentration/ dose	unknown (no score)	unknown (no score)	0.2-5 µg/cm² (score 0)	unknown (no score)	<u>Omnipod</u>: ~0.53µg/cm² (score 0) <u>FreeStyle Libre:</u> unknown (no score)	unknown (no score)

Reference	(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)
Repeated exposure[10]	≥ once/daily (score 2)	unknown (no score)	≥ once/daily (score 2)	≥ once/daily (score 2)	≥ once/daily (score 2)	≥ once/daily (score 2)
Number of exposures[11]	Case 1: ~30 (score 0) Case 2: ~120-150 (score 2)	unknown (no score)	5 patients: unknown (no score) 4 patients: ~14-60 (score 0) 3 patients: ~180-540 (score 2)	unknown (no score)	Omnipod: 4 (score 0) FreeStyle Libre: ~180 (score 2)	Case 1: ~120 (score 2) Case 2: ~360 (score 2) Case 3: ~180 (score 2), FreeStyle Libre 1 (score 0), Omnipod Case 4: ~180 (score 2), FreeStyle Libre >210 (score 2), Omnipod
Additive exposure index	n.d.[12]	n.d.	6 patients: n.d. 4 patients: 2 3 patients: 4	n.d.	Omnipod: 2 Freestyle Libre: n.d.	n.d.
EXPOSURE	n.d.	n.d.	**low exposure**	n.d.	Omnipod: **low exposure**[13] Freestyle Libre: n.d.	n.d.
Resulting clasification	**Skin Sens. 1**	**Skin Sens. 1**	**Low frequency Low exposure** **Skin Sens. 1**	**Skin Sens. 1**	**Low frequency Low exposure** **Skin Sens. 1**	**Skin Sens. 1**

Altogether, due to the comparatively low number of reported cases and insufficient exposure data, the human data do not allow for the reliable allocation of IBOA to a sub-category (see Table 10 for details).

[10] The exposure that takes place upon use of medical devices such as insulin patch pumps and continuous glucose monitoring systems cannot be fully compared with the criteria described in the CLP Guidance (ECHA, 2017). The "≥ once/daily" criterion seems to apply to situations where every day one or even more exposures occur. Continuous contact over several days without interruption is not reflected by this criterion but in the view of the DS justifies the high score of 2 since exposure is more intense than through repeated, but short-time daily contact.

[11] The DS considers every day on which the respective medical device is in contact with the skin as one exposure. For example: one month equals 30 exposures.

[12] n.d.: not-determinable

[13] It is noted that the patient had already developed skin reactions following contact to the FreeStyle Libre device.

These results are supported by an LLNA test, in which SI values between 4 and 14 (i.e. >>3, the CLP cut-off value for classification as Skin Sens. 1) were observed; it is however unclear whether the test item still contained IBOA or rather its degradation products (RCC, 2012).

10.5.5 Conclusion on classification and labelling for skin sensitisation

Based on the overview presented in the previous sections, the DS proposes to classify IBOA as a **skin sensitiser, category 1** (**Skin Sens.1; H317 – May cause an allergic reaction**) without sub-categorisation. No Specific Concentration Limit (SCL) is proposed.

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.

The EC3 may be extrapolated using all sets of available data from the LLNA with isobornyl acrylate (RCC, 2012) by means of: a) linear regression, b) quadratic regression or c) log linear extrapolation. These methods allow to calculate a continuous dependent variable *Y* (in this case a SI at a given concentration as a mathematical function of an independent variable *X* (in this case concentrations of isobornyl acrylate used in LLNA).

a) With the linear regression, the following equation was derived to calculate a value of SI at concentrations not tested in the assay: SI = 1.5736 + 0.8921 x concentration. Using this equation it has been calculated that EC3, the concentration needed for 3-fold increase of SI, is equal 1.6%, thus lower than 2%, which is an upper limit for classification to category 1A. However, it is noted that a typical dose-response of population exposed to increasing doses of toxic chemical is a sigmoid dose-response curve, not a straight line. Thus other ways of extrapolation, such as a quadratic regression or a log linear extrapolation, could be more appropriate.
b) With the quadratic regression, the following equation was derived to calculate a value of SI at concentrations not tested in the LLNA: SI = - 0.041 + 1.4479 x concentration - 0.021 x (concentration)^2. Using this equation, EC3 was calculated to be 2.2%, thus above 2%, which is upper limit for classification to category 1A.
c) With the log linear extrapolation, the following formula was applied (Ryan *et al*., 2007) to the two lowest concentrations from the LLNA with isobornyl acrylate (a = 10, b = 14.07, c = 5, d = 4.07):

$$EC3_{ex} = 2^{\wedge}\left\{\log_2(c) + \frac{(3-d)}{(b-d)} \times \left[\log_2(a) - \log_2(c)\right]\right\}$$

Coordinates:

(a = dose concentration for next to lowest SI above 3, b = next to lowest SI above 3)

(c = dose concentration for lowest SI above 3, d = lowest SI above 3)

Giving an EC3 value of 4.4%, thus above 2%, which is upper limit for classification to category 1A. The calculated EC3 value of 4.4% is closed to the lowest concentration of 5% used in LLNA, which produced an SI of 4.07%. The extrapolated EC3 value is thus close to the actual data. The calculation of EC3 using the interpolation method (Basketter *et al.*, 1999) and an extrapolation method (Ryan *et al.,* 2007) for the same set of substances has shown that only 9 out of 21 substances (41%) the interpolated and extrapolated EC3 values would lead to the same dermal sensitisation category for those test substances (Gould and

Taylor, 2011). This analysis (Gould and Taylor, 2011) suggests that interpolation and extrapolation of EC3 values based on results of LLNA for the same substance may lead to different skin sensitisation potency estimates.

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.

10.6 Germ cell mutagenicity

Not evaluated in this dossier

10.7 Carcinogenicity

Not evaluated in this dossier

10.8 Reproductive toxicity

Not evaluated in this dossier

10.9 Specific target organ toxicity-single exposure

Not evaluated in this dossier

10.10 Aspiration hazard

Not evaluated in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier

13 ADDITIONAL LABELLING

Not applicable

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15 ANNEXES

Annex I