Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate

EC Number: 201-297-1
CAS Number: 80-62-6

CLH-O-0000006852-69-01/F

Adopted

18 March 2021

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8 October 2020

CLH-O-0000006852-69-01/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: **methyl methacrylate; methyl 2-methylprop-2-enoate methyl 2-methylpropenoate**

EC Number: **201-297-1**

CAS Number: **80-62-6**

The proposal was submitted by **France** and received by RAC on **28 February 2019.**

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

PROCESS FOR ADOPTION OF THE OPINION

France 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 **6 May 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **5 July 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Normunds Kadiķis**

Co-Rapporteur, appointed by RAC: **Tiina Santonen**

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 **18 March 2021** 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	607-035-00-6	methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate	201-297-1	80-62-6	Flam. Liq. 2 Skin Irrit. 2 Skin Sens. 1 STOT SE 3	H225 H315 H317 H335	GHS02 GHS07 Dgr	H225 H335 H315 H317			D
Dossier submitters proposal	607-035-00-6	methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate	201-297-1	80-62-6	**Add** Resp. Sens. 1	**Add** H334	**Add** GHS08	**Add** H334			
RAC opinion	607-035-00-6	methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate	201-297-1	80-62-6	**Add** Resp. Sens. 1	**Add** H334	**Add** GHS08	**Add** H334			
Resulting Annex VI entry if agreed by COM	607-035-00-6	methyl methacrylate methyl 2-methylprop-2-enoate methyl 2-methylpropenoate	201-297-1	80-62-6	Resp. Sens. 1 Flam. Liq. 2 Skin Irrit. 2 Skin Sens. 1 STOT SE 3	H334 H225 H315 H317 H335	GHS02 GHS08 Dgr	H334 H225 H335 H315 H317			D

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

Respiratory sensitisation was the only endpoint assessed by the dossier submitter (DS) France for harmonised classification and labelling (CLH). The DS proposed to classify methyl methacrylate (MMA) as Resp. Sens. 1; H334.

As part of this weight of evidence assessment, the DS also briefly summarised the animal and human data for skin sensitisation, for which MMA has an existing classification as Skin Sens 1; H317.

In order to distinguish between potential irritative and sensitising properties of MMA after inhalation, the DS also presented data on respiratory irritation. MMA has been reported to have a strong, readily detectable smell at concentrations between 32 and 65 ppm, and irritation has been observed at concentrations exceeding 100 ppm, being "very definite" at concentrations between 170 to 248 ppm. In addition to skin sensitisation, MMA has existing harmonised classifications as STOT SE 3; H335 and Skin Irrit. 2; H315. Data on toxicokinetics was also presented by the DS in the CLH dossier.

There are no validated experimental animal assays with which to assess respiratory sensitisation. Therefore, the data available for this endpoint and included in the CLH dossier consisted of reports on diagnosed occupational asthma cases and epidemiological studies on human respiratory sensitisation. The case reports were both from the scientific literature and extracted from national occupational disease databases.

National Occupational databases

Forty-three case reports on respiratory sensitisation were extracted by the DS from the French National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P) database (n=43; 2001-2017). For these cases, the causal link between occupational asthma and MMA exposure had been determined as a "high level of attributability", meaning a high, direct and essential link, or "Moderate level of attributability", meaning a possible link or direct but not essential link. There were an additional 23 case reports extracted from the UK Surveillance of Work Related and Occupational Respiratory Disease (SWORD) database (1989-2017), where occupational asthma had been reported by chest physicians. There was one case report in the Occupational Physicians Reporting Activity (OPRA) database, reported by an occupational physician (1996–2017). Four additional methyl methacrylate specific case reports were extracted from the Finnish Institute of Occupational Health's (FIOH) database (1997–2018). This database includes the Finnish occupational asthma cases, all of which are confirmed at FIOH. These four asthma diagnoses were confirmed by a positive response in the specific inhalation challenge (SIC), which RAC notes is widely considered a reference standard in the diagnosis of occupational asthma when performed adequately (Suojalehto *et al.,* 2019; Vandenplas *et al*., 2014). Two of these SIC-responses were reported as late reactions (meaning after 1-8 h of exposure), one was a dual reaction (meaning both early and late reactions) and one was an early reaction (meaning within 1 h of exposure).

These case reports from European databases cover workers of both sexes representing different ages and who are involved in a number of occupational sectors – mainly nail technicians, dental technicians, car industry workers, polystyrene industry workers and painters. More detailed information on the extracted cases is provided in Annex 1.

Reports of National Authorities

In addition to the aforementioned case reports, National Authorities reported the following:

- One case was accepted within the last five years by the Belgian Fund of Occupational Diseases (Fedris) for compensation of an MMA-induced occupational asthma.
- Three cases of occupational asthma were reported to the Netherlands Centre for Occupational Diseases (NCOD) due to exposure to acrylates between 2005 and 2017.
- The Swedish Work Environment Authority (SWEA) received a small number of reports of respiratory complaints during 2008–2018.

However, in the Dutch and Swedish cases, methyl methacrylate was not specified as the causative agent.

Scientific literature

From the scientific literature, one cohort study (Marez *et al*., 1993) was included, reporting increased incidence of chronic cough and mild airway obstruction linked with an occupational exposure to MMA (not related to smoking habits). There are several case reports published in the literature (Pickering *et al*., 1986; Savonius *et al*., 1993a,b; Uriarte *et al*., 2013; Roth *et al*., 2017; Scherpereel *et al*., 2004), which described asthmatic reactions and respiratory sensitisation. However, it was not possible to conclude that the symptoms of all the subjects resulted specifically from exposure to methyl methacrylate.

Other evidence

In a survey by Röhm GmbH in 1994 (described by the DS as a personal communication), 211 male workers in acrylic sheet production and exposed to methyl methacrylate were included in a medical examination. No cases of MMA-related skin or respiratory sensitisation were observed. Reversible irritation of the eyes and the upper respiratory tract were observed.

Following a request by the DS, several SAR models and the DK QSAR Toolbox were run by RIVM, but the results were inconclusive. The DS mentioned that in the ECHA Guidance on Information Requirements and Chemical Safety Assessment, it is stated that QSAR models are known not to be predictive, as there are no validated test methods available to assess this type of endpoint.

Conclusion of the DS

The DS viewed the evidence that MMA is a skin sensitiser (current harmonised classification Skin Sens. 1; H317) as indicative of its potential to cause respiratory sensitisation in humans. In addition, MMA is readily absorbed via all routes of exposure, including the inhalation route, although it is rapidly metabolised and excreted. The DS considered that there is evidence from human data that MMA induces asthma, and that it should therefore be classified as a respiratory sensitiser. The DS acknowledged that methyl methacrylate is a (respiratory) irritant (current harmonised classification STOT SE 3; H335 and Skin Irrit. 2; H315), and therefore it may be difficult to distinguish the mechanism that leads to asthma. They mentioned that according to CLP however, *"the condition will have the clinical character of an allergic reaction"*, and that is the case here, and further noted that *"immunological mechanisms do not have to be demonstrated".* Sub-categorisation was not proposed by the DS, as there is no adequate information on the level of exposure mentioned in the case reports and the frequency of this pathology.

Comments received during consultation

Four comments were received during the consultation, three from Member State Competent Authorities (MSCAs) and one from a Company-Manufacturer. All three MSCAs supported classification as Resp. Sens. 1 without sub-categorisation. One MSCA also gave information on two publications, of which Walters *et al*. (2017) supports the association between occupational asthma and exposure to acrylates, and DeKoven *et al*. (2017) who reported an increasing trend in the incidence of allergic contact dermatitis in nail salon workers. They pointed out that this reflects a more general trend in nail salon workers due to occupational (meth)acrylate exposure and was considered by them to be of concern also with regard to potential new cases of work-related respiratory sensitisation among nail technicians.

A Company-Manufacturer disagreed with the proposed classification and instead was of the view that the current Annex VI entry should remain unchanged. They argued that the weight-of-evidence approach in the CLH proposal was not balanced and not scientifically justified. In a detailed report, they presented their argumentation for not classifying MMA as a respiratory sensitiser. This was based on three main arguments: 1) obligatory evidence for a biphasic mode of action was not included, 2) a valid "causation" of the development of asthma in relationship to MMA exposure was not determined, and 3) a clear differentiation distinguishing between respiratory irritant effects (for which this substance is already classified) against the claimed respiratory sensitisation effects was not provided in sufficient detail.

They provided an alternative assessment, in their view following the scientific standards of ECHA [Guidance], the European Commission's Scientific Committee Health and Environment Emerging Risk (SCHEER) and based on a broader database than that presented in the CLH report. They concluded that, there is a lack of confidence in the CLH proposal that MMA is a causative agent for occupational asthma and were of the view that instead, all available evidence reviewed in the literature of sufficient strength confirmed that MMA only has the potential to aggravate asthmatic symptoms in pre-existing asthmatics.

They also pointed out literature that had been missing from the CLH proposal:

- EU Risk assessment (ECB, 2002), which concluded that there was "*no convincing evidence that MMA is a respiratory sensitiser in humans"* and viewed that "*possible non-specific asthmatic responses due to respiratory tract irritation cannot be excluded and labelling with R37 is sufficient for the protection of humans"*.
- SCOEL (2006), which similarly concluded that "*MMA is clearly a sensory irritant towards the respiratory tract and in the majority of these cases "asthmatic" respiratory responses have been attributed to exposure to transiently high concentrations of MMA that may have resulted in respiratory irritation in individuals with normal airway responsiveness, or perhaps in some cases with pre-existing, generally hyperreactive airways."* And that *"overall, there is no convincing evidence that methyl methacrylate is a significant inducer of asthma in humans".*
- A review by Borak *et al.* (2011), which also concluded that "*the weight of evidence, both experimental and observational, argues that MMA is not a respiratory sensitizer*".
- Pickering *et al*. (1993), based on which risk assessment reports by the EU and OECD concluded: "*From these studies there is no convincing evidence that MMA is acting as a respiratory sensitizer, however, there is clear evidence of acute respiratory irritation, at high exposure levels"*.
- Several scientific papers (listed in the public attachment to their comment) that the Company-Manufacturer considered of low reliability.

The DS noted in their reply as follows (with some typos corrected): "*The asthma linked to an occupational exposure to methyl methacrylate is recognised in France by the French National*

Research and Safety Institute for the Prevention of Occupational Accidents and Diseases (INRS) since 1987. *Additionally, all the cases reported in the dossier especially from the RNV3P (The National Network for the Monitoring and Prevention of Occupational Diseases) were reported by specialized occupational practitioners who clearly linked an occupational exposure to MMA with different kinds of asthma. Moreover, only the cases with a high attributability were included*".

RAC accepts that evidence for a biphasic mode of action was not included in the CLH report. However, for the development of the RAC opinion, two additional publications were considered:

1. Walters *et al*. (2017), which supports an association between occupational asthma and exposure to predominantly methyl methacrylate in eight cases reported to the UK SHIELD surveillance scheme between 1989 and 2014.
2. A recent study by Suojalehto *et al*. (2020), supplemented with additional information received directly from the authors, providing further evidence of occupational asthma in six subjects verified to have predominantly been exposed to methyl methacrylate (see "Further discussion" below). The occupational asthma diagnoses in Suojalehto *et al*. (2020) were confirmed by placebo-controlled SICs.

It should also be noted that in the case of low molecular weight substances, which do not cause IgE-mediated responses, demonstration of causality is always more difficult than in the case of allergens resulting in clear IgE-mediated responses.

More detailed responses to the Company-Manufacturer's comment are given in the response to comments (RCOM) document annexed to this opinion.

An additional *ad hoc* consultation was held in February 2020 on the Suojalehto *et al.* 2020 publication (for further details, see "Discussion of additional data" below). In this consultation, two further MSCAs supported the classification proposal. In addition, several Company-Manufacturers, Company-Downstream users, Industry or trade associations and Company-Importers disagreed with the proposal. Their main concerns were related to 1) lack of data available to assign causality to specific substances, 2) uncertainty of potential co-exposure and irritating peak exposures, and 3) lack of trust in the original WoE approach of the classification proposal. In addition, several comments concerned the lack of methyl methacrylate-induced asthma cases in selected companies or use sectors.

Concerning the data available to assign causality to specific substances, potential co-exposure and peak exposures causing irritation, RAC considers the publication by Suojalehto *et al.* (2020), with the additional information received from the authors, to provide relevant evidence. RAC agrees that the original classification proposal had shortcomings. However, the Committee considers that the detailed comments received also in the original public consultation have been appropriately taken into account. Subsequently, additional key elements were identified and evaluated by RAC to form the current RAC opinion.

RAC notes that case reports on methyl methacrylate-induced occupational asthma, for example in the European occupational diseases databases, particularly concern nail beauticians and dental and medical prosthesis technicians. It should be noted that specific exposure conditions, not applicable to all uses, may play a role. Therefore, lack of MMA-induced asthma cases in the particular use scenarios of specific companies or sectors does not demonstrate a lack of intrinsic respiratory sensitising potential by MMA. Even if occupational asthma induced by methyl methacrylate is mostly seen in a special group of users, such as in the dental or cosmetic sector, it indicates an intrinsic property to induce respiratory sensitisation, which must be considered relevant for classification. In addition, it is quite possible that MMA-induced occupational asthma cases are underdiagnosed and underreported.

More detailed responses to all concerns raised in the *ad hoc* consultation are provided in the targeted consultation response to comments document.

Discussion of additional data

After the original public consultation, during the development of its opinion, RAC was made aware of a new publication (Suojalehto *et al*., 2020). In addition, supplementary data and information, which had not been included in this publication, were received from the authors in response to ECHA's information request D(2021)0116 (Annex 5).

In this study, acrylate exposure was clearly connected with occupational asthma by the authors. The characteristics of acrylate induced occupational asthma were evaluated in a large series of cases (n=55 for acrylates), and were compared with the characteristics of occupational asthma induced by other low molecular weight (LMW) agents (n=418 for other LMW agents, of these n=125 for isocyanates). The study examined an international, multicentre retrospective cohort of subjects with occupational asthma ascertained by positive, placebo controlled SICs (between January 2006 and December 2015). The subjects' jobs and exposures, clinical and functional characteristics, and markers of airway inflammation were analysed. The SICs aimed to recreate an exposure comparable to that at the subjects' workplace. The aim of the placebo test was to expose the subjects with a similarly irritant, non-sensitising agent to rule out asthmatic responses due to irritation. The methodology of SIC conformed with international recommendations (Vandenplas *et al*., 2014).

In the SICs, the exposures were kept well below known respiratory irritant concentrations and relevant OELs, but MMA concentrations were not measured in any of the SICs included in Suojalehto *et al.* (2020). However, 3/6 of the MMA-cases in this publication were diagnosed at the Finnish Institute of Occupational Health, where a stable SIC protocol for two-component MMA-based methacrylate products has been used since 2000, and detailed information on the exposure levels in SICs exist (Annex 5: response from Suojalehto *et al.* to ECHA request D(2021)0116). Data of five MMA measurements during 2007-2020 were available from very similar SICs, using the same kind of products, the same chamber and having similar conditions such as humidity, temperature and ventilation. In these SICs, the measured concentrations were 0.56, 3.6, 5.1, 5.6 and 13 mg/m^3 (time-weighted averages; TWAs). The highest value was reported by the authors to be an outlier, which might be due to contamination in the sensitive analysis. According to the authors, it is extremely unlikely that any of the three Finnish MMA cases in Suojalehto *et al.* (2020) were exposed to more than the highest measured level (13 mg/m^3) during the SIC. Due to similar products and SIC protocols, it is likely that the exposure levels in two further MMA cases, diagnosed in other units, were comparable to those from which the measured concentration data were available. In the third case, which was diagnosed in other units, the patient ground a recently hardened prosthesis during the SIC. Air measurements in similar SICs at FIOH have produced about 1/10 of the MMA concentration measured during mixing of liquid and powder. Most international 8 h OELs for MMA range from 100 to 410 mg/m^3 (GESTIS International limit values database), being around 200 mg/m^3 in many European countries. Exceptions to the aforementioned are Finland (42 mg/m^3), Latvia (10 mg/m^3) and Japan (8.3 mg/m^3), based on information in GESTIS.

As mentioned, the measurement data available for the SICs were average levels, and therefore the presence of MMA-peaks could not be excluded. However, RAC considers it unlikely that peaks would have been of paramount importance in the cases described in Suojalehto *et al*. (2020). The SICs were placebo-controlled, and data is available also on negative responses in similar SICs performed with MMA on asthmatics, described in more detail further below (p. 11). Of the 55 subjects with ascertained acrylate occupational asthma in Suojalehto *et al.* (2020), six had been predominantly exposed to MMA and tested positive specifically for this substance (Annex 5: response from Suojalehto *et al*. to ECHA request D(2021)0116; "predominantly" meaning that

the main component of the products used was MMA, as opposed to mixed-exposures with other (meth)acrylates). In the Finnish cases (n=3), experts were able to verify from the original product information that they were two-component, self-curing methacrylate products containing MMA as their main ingredient. Based on the product information provided by the other centres (n=3), they were also able to conclude that these patients had used two-component MMA products to make prostheses.

Three of these six subjects had a delayed reaction in the SIC, two had a bi-phasic reaction (meaning both early and delayed), and one had an early reaction. While irritant effects cannot always be ruled out in early reactions, late and bi-phasic reactions in adequately performed SICs are considered by experts a hallmark of an immunological response. Two of these six subjects were dentists, three were dental and medical prosthesis technicians, and one was a nail beautician using MMA for acrylic nails.

As supporting data to the above, the table below presents 55 acrylate occupational asthma subjects, of which 24 had asthma considered by the authors to be ascertained as methacrylate induced. Of these, 20/24 had either late or bi-phasic positive SIC reactions. Apart from the six subjects that had specifically used MMA, most of these 24 were occupationally exposed to mixtures of methacrylates.

The study also showed that acrylates may induce occupational asthma through different immunologic mechanisms than other LMW agents, as asthma induced by acrylates had differing phenotypic characteristics, and in fact showed some characteristics that have previously been linked to occupational asthma caused by high molecular weight agents. However, the mechanism for acrylate induced asthma is still unknown, but it is seen by experts as clearly immunological. This view is supported also by this study.

In addition, an "asthma hazard index" was generated using the most recent iteration of a QSAR model by Jarvis *et al*. (2015). The index ranged from 0 to 1, 1 flagging the highest probability that the compound has respiratory sensitisation potential, based on its chemical structure (not its volatility). Using this model, the asthma index for MMA was 1, implying that the QSAR interprets its chemical structure as having the features required to cause asthma by sensitisation. The model's external statistics suggested that applying a cut-off point of 0.39 enables discrimination of respiratory sensitisers from controls with a sensitivity of 90% and a specificity of 96%.

Table**: Supplementary data to (Suojalehto et al., 2020), received from the authors.**

Table 2. Functional characteristics of subjects with occupational asthma caused by cyanoacrylates, methacrylates and plain acrylates

	Cyanoacrylates (n=28)	Methacrylates (n=24)	Acrylates (n=3)	P-value
Baseline spirometry:				
FVC, % pred[a]	95.8 (87.0-102.1)	97.0 (89.8-111.2)	92.0 (86.0-93.5)	0.300
FEV_1, % pred[a]	92.0 (83.0-99.1)	96.0 (83.8-102.8)	90.0 (76.5-93.0)	0.440
FEV_1 <80%	5 (17.9)	3 (12.5)	1 (33.3)	0.480
FEV_1/FVC[a]	81.3 (76.5-85.5)	80.5 (75.8-84.0)	79.0 (70.5-85.5)	0.810
Airflow obstruction[b]	2 (7.1)	0	1 (33.3)	0.080
Baseline level of NSBH:	(n=25)	(n=20)	(n=3)	0.510
Absent	8 (32.0)	8 (40.0)	0	
Mild	10 (40.0)	8 (40.0)	3 (100.0)	
Moderate-to-severe	7 (28.0)	4 (20.0)	0	
Post-challenge change in NSBH[c]	(n=15)	(n=6)	(n=3)	
Pre/post-SIC NSBH ratio[a]	2.0 (1.0-3.9)	1.5 (0.6-2.0)	3.6 (2.1-3.8)	0.710
Pattern of bronchial response to SIC	(n=27)	(n=24)	(n=3)	
Isolated early	6 (22.2)	4 (16.7)	2 (66.7)	0.160
Isolated late	15 (55.6)	8 (33.3)	1 (33.3)	0.320
Both early and late components	6 (22.2)	12 (50.0)	0	0.070

Data are presented as n (% of available data) unless otherwise specified. Values in boldface are statistically significant. FEV_1: forced expiratory volume in one-second; FVC: forced vital capacity; NSBH: nonspecific bronchial hyperresponsiveness; SIC: specific inhalation challenge.

[a] Median value with interquartile range (IQR) within parentheses;

[b] Airflow obstruction defined by a FEV_1 <80% predicted value and a FEV_1/FVC ratio <70%;

[c] See ref (24) for the threshold values used for grading the level of NSBH.

Walters *et al*. (2017) described a series of occupational asthma cases caused by acrylic compounds, extracted from a UK-based regional surveillance scheme between 1989 and 2014. This study included 20 affected patients whose occupational asthma diagnoses were confirmed by OASYS (Occupational Asthma SYStem) analysis of serial peak flow measurements. Furthermore, three positive SIC tests were included. These cases were not included in Suojalehto *et al*. (2020; see Annex 5: response from Suojalehto *et al*. to ECHA request D(2021)0116).

Of these 20 patients in Walters *et al.* (2017), methyl methacrylate was reported as the predominant causative agent for eight patients. For six of these eight, MMA was reported as the only causative agent, but for the other two patients a mixture of MMA and cyanoacrylate was reported. Two of these diagnoses had been confirmed also with SIC, but the SIC methodology was not described. In both of these cases, MMA was mentioned as the only causative agent; the occupations of these patients were plastic moulder (prosthetic limbs) and orthopaedic theatre nurse. However, one of these patients (plastic moulder) had also been occupationally exposed to methylene diphenyl diisocyanate (MDI), to which he also reacted positively in the SIC.

Regarding the differentiation between irritating and sensitising effects of MMA, it is important to note that also negative responses (i.e. no asthmatic response) in the SIC are seen in asthmatics tested for MMA. Although not related to the cases in Suojalehto *et al.* (2020), the authors also provided information on negative responses in SIC in patients tested for MMA (Annex 5: response from Suojalehto *et al.* to ECHA request D(2021)0116). At the Finnish Institute of Occupational Health, during 2013-2019, seven patients were tested due to occupational asthma suspicion possibly related to MMA exposure with negative SIC results. Five of them already had an asthma diagnosis. Altogether 16 challenges (12 challenges to patients with existing asthma diagnosis) were performed with negative results with products containing only or predominantly MMA. In 11/16 of these cases, the product tested contained > 90-95% MMA or MMA and non-sensitising solvents. In 3/16 cases, the exposure was to a mixture of 50-100% MMA and ≤ 10% TMDMA. In 1/16 cases, a mixture of 50-70% MMA and < 10% triethyleneglycol dimethacrylate was used, and in 1/16 cases a mixture of 50-70% MMA and other methacrylates was used. In all of these cases, the SIC aimed to recreate an exposure comparable to that at the patient's workplace. RAC considers this information to demonstrate that it is not plausible that MMA induces reactions in asthmatics purely due to irritation.

Assessment and comparison with the classification criteria

No animal data are available regarding respiratory sensitisation due to lack of appropriate tests for this hazard class. The DS provided information on a number of published human occupational studies including one epidemiological cohort study on workers occupationally exposed to MMA (Marez *et al*., 1993), one survey with medical examination of workers involved in acrylic sheet production (Röhm GmbH, 1994) and six case studies of exposure of single workers exposed to MMA in differing applications (Pickering *et al*., 1986; Savonius *et al.*, 1993a and 1993b; Scherpereel *et al.,* 2004; Uriarte *et al*., 2013; Roth *et al*., 2017).

All of them gave indications of a positive correlation between MMA exposure and occupational asthma and/or deterioration of lung functions and related lung disease symptoms, with the exception to the survey on workers involved in acrylic sheet production (Röhm GmbH, 1994). In this latter survey, 211 male workers were exposed to MMA concentrations that varied from 3 to 40 ppm (personal sampling measurements performed at the time of the study, according to TRGS 402 and calculated as 8 hours TWA geometrical mean concentration). It was reported that previously 8 h TWA concentrations had been between 10 and 70 ppm. No cases of MMA exposure related to skin or respiratory sensitisation were observed. Observation of irritation of the eyes and the upper respiratory tract was limited to acute and reversible reactions after short-term peak exposures at concentration levels exceeding 100 ppm (410 mg/m^3). No clinical symptoms of lung diseases were reported.

Marez *et al*. (1993) investigated a cohort of 40 workers in two factories with either less or more than 10 years exposure to MMA and compared it with a control group of 45 workers which had not been exposed to MMA. The study included a questionnaire, spirography and an evaluation of the occupational air concentration of MMA by passive samplers (mean air concentration detected: 18.5-21.6 ppm). Examination of the lung function parameters showed an increased incidence of

chronic cough (20% in the exposed group compared with 1% in controls) and mild airway obstruction, neither of which were attributed to smoking. Spirometic values at the beginning of the work shift were similar in both groups, but a mild airway obstruction appeared during the work shift for the exposed group. The study did not give any clear indication of occupational asthma symptoms.

The case study by Pickering *et al.* (1986) reported on a 56 year old female working as a nurse in a hospital operating theatre with at least 7 years of experience in working with bone cements consisting of poly(methyl methacrylate) and methyl methacrylate liquid. The patient developed respiratory symptoms characterised by a persistent cough, wheeziness and breathlessness. These symptoms were associated with periods at work and resolved on rest days or on leave. A controlled exposure to the cements and MMA, under simulated working conditions, resulted in a delayed asthmatic reaction occurring 6 h after exposure with a maximum fall in forced expiratory volume in 1 second (FEV1) of 25% 13 h after the challenge.

Savonius *et al.* (1993a and 1993b) described three cases reportedly of respiratory sensitisation due to exposure to MMA. A 48 year old woman involved in plate engraving was exposed during the use of a glue and had developed respiratory distress at work with strain, sneezing, rhinorrhoea and stuffiness. Challenge to the implicated glue caused a maximal 24% fall in Peak Exploratory Flow (PEF) values and her symptoms persisted even after she changed to using cyanoacrylate glue. Her symptoms persisted and she had to quit her job. The second case was a 32 year old man involved in the assembly of hearing devices showing a small maximal 15% decrease in PEF values following the grinding of "a piece of methacrylate" in an exposure chamber. The third case was a 46 year old woman who had worked for about 20 years as a dental technician. She experienced a feeling of tickling in her throat, yawning, cough, tiredness and chest tightness; the symptoms subsided on sick leave and vacations but recurred within a week after returning to work. Simulated occupational exposures to "methacrylate powder and methacrylate liquid" for 30 minutes resulted in a maximum reduction of 26% in the PEF value. A skin prick test to "methacrylate" was negative. The authors of the study concluded that it is not possible to firmly conclude that the symptoms resulted from exposure to methyl methacrylate.

Scherpereel *et al. (*2004) reported on two cases of hypersensitivity pneumonitis in dental technicians following an inhalation exposure to MMA. Firstly, a 24 year old female dental technician exposed to MMA for 6 months developed severe dyspnoea and hypoxemia and had to quit her job. The second case was a 20 year old woman – a student dental technician hospitalised for acute respiratory distress. She also showed hypoxemia.

Uriarte *et al.* (2013) reported a case of a 48 years old man with no history of atopy who worked as a professional plumber for over 30 years and had sought medical advice for progressive dyspnoea and dry cough during the last 3 years. His symptoms were triggered at work and persisted outside work. After performing a SIC for methyl methacrylate, the asthma reaction following an exposure to the substance was confirmed.

Roth *et al.* (2017) reported a case of an orthopaedic surgeon with no history of lung disease, who developed cough and dyspnoea. The effects were attributed to his occupational exposure to MMA, which is an important component of bone cement. The patient was diagnosed with asthma by spirometry and a bronchial provocation test with methacholine. The patient was diagnosed with work related disease, which was recognized by the industrial injury board.

According to the industry, the asthmas attributed to bone cement may also have been caused by gentamicin, an antibiotic medicine present in bone cement that has a self-classification as Resp. Sens. 1, H334. There is, however, no information available on the data this self-classification is based on, and RAC was not able to identify literature related to respiratory sensitisation by gentamicin. Gentamicin is also administered via inhalation as a medication, including long-term treatment in cystic fibrosis patients. Systemic gentamicin treatment can in

rare cases cause an anaphylactic shock in patients. It is also a known skin sensitiser. The only study found related to gentamicin and asthma concluded: "Substantial obstructive reactions may occur in some asthmatic subjects after inhalation of gentamicin. The reactions appear to be non-immunological in nature and may be due to an irritant effect of the drug vehicle" (Dally *et al*., 1978). Overall, in the light of the information available, RAC does not consider gentamicin as a likely cause for asthmas induced by bone cements.

In addition, there are several case reports on respiratory sensitisation from European occupational disease databases. For most of them, there is minimal contextual information available, and RAC could not evaluate them. For the four case reports extracted from the Finnish Institute of Occupational Health database, it was reported that the asthma diagnoses were based on a positive response in the SIC. In two of these cases, the reactions were late (meaning that they occurred after 1-8 h of exposure), one was a dual reaction (meaning both early and late reactions) and one was an early reaction (meaning within 1 h of exposure). In particular, the late and dual reactions strongly argue for an immunological response rather than one due to respiratory irritation. Three of these four Finnish Institute of Occupational Health cases were also included in Suojalehto *et al.* (2020).

In the study reported by Suojalehto *et al.* (2020), acrylates were clearly linked with occupational asthma using placebo-controlled SIC exposures. Of the 55 subjects in whom acrylate related occupational asthma was ascertained, 24 tested positive for methacrylates and six tested positive specifically for methyl methacrylate. Five of these six subjects presented a delayed or bi-phasic (meaning early and delayed) reaction in the placebo-controlled SICs, considered by experts to strongly indicate an immunological response. One subject presented an early reaction. It should be noted that even though irritant effects cannot always be ruled out in early reactions, this does not mean that they are necessarily due to them in adequately performed SICs. In addition to a placebo-control exposure, also measurement of pulmonary function can be used to distinguish sensitisation and irritation also in early reactions in SIC. Moreover, an increase in inflammatory markers supports the diagnosis. In the SICs reported by Suojalehto *et al.* (2020), placebo exposures were conducted for the subjects. The aim of the placebo test is to expose the subject with a similarly irritant, non-sensitising agent. If the subjects' positive reactions would have been due to respiratory irritation, they should also have had a positive reaction in the placebo exposure.

Importantly, negative responses in the SIC are also seen in asthmatics tested for MMA, as described above. This clearly indicates that it is not plausible that methyl methacrylate purely induces reactions in asthmatics due to its respiratory irritant properties.

RAC notes that the relatively low number of MMA related occupational asthma cases reported in the scientific literature or occupational disease databases should not be seen as evidence of low prevalence. As none of the acrylates are classified for respiratory sensitisation, most occupational physicians are unlikely to suspect the acrylates or more specifically methyl methacrylate as a causative agent in a patient's asthma. Therefore, RAC considers it possible that MMA occupational asthma cases are underdiagnosed and are therefore also under-reported.

RAC is of the opinion that the existing cases reviewed here, already reliably attributed to methyl methacrylate, clearly demonstrate its potential to induce respiratory sensitisation.

On the other hand, it is known that methacrylates cross-react, and as acrylates are often used as mixtures, in such cases, it can be difficult to establish in clinical studies, which compound specifically had induced the sensitisation, or whether it was due to mixed exposure. However, as presented earlier, six individual cases could be identified in the cohort of Suojalehto *et al*. (2020), where the predominant occupational exposure was known to be specifically to MMA (based on careful expert judgment of the ingredients of the products used), and those patients had a positive reaction to MMA in the SIC. These subjects had occupations as dentists, dental and medical prosthesis technicians, and nail beauticians. It should be noted that dental and medical

prosthesis technicians and nail beauticians continue to use liquid-powder mixtures, of which the liquid is typically 100% MMA. Also the independent dataset by Walters *et al*. (2017) gives support that MMA has potential to induce respiratory sensitisation in humans. Due to uncertainty regarding the diagnostic methodology used, RAC considers Walters *et al*. (2017) as supporting information.

Finally, RAC would like to note that a negative result in a skin prick test should not be interpreted as a negative result for respiratory sensitisation by MMA. It is well known that methyl methacrylate and other low molecular weight agents (such as diisocyanates) tend to systematically produce negative results in the skin prick test (Suojalehto *et al*., 2020). Nevertheless, MMA is a known skin sensitiser and has an existing harmonised classification as Skin Sens. 1; H317. Although this is not proof of its respiratory sensitising potential, the intrinsic skin sensitising property of the molecule is established. In addition, MMA is volatile (vapour pressure 37 hPa at 20 °C), meaning that exposure by inhalation is relevant.

The CLP criteria for classification of a substance as the respiratory sensitiser are the following:

Table 3.4.1

Hazard category and sub-categories for respiratory sensitisers

Category	Criteria
Category 1	Substances shall be classified as respiratory sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity; and/or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests (1). Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests (1). Severity of reaction may also be considered.
(1) At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.	

On human evidence, the regulation states: "*Evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. <u>However, immunological mechanisms do not have to be demonstrated</u>.*"

And furthermore: "*The evidence referred to above could be:*
***(a)** clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include: (i) in vivo immunological*

test (e.g. skin prick test); (ii) in vitro immunological test (e.g. serological analysis); (iii) studies that indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects; (iv) chemical structure related to substances known to cause respiratory hypersensitivity;
(b) *data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction."*

Moreover, it is stated that "*The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own*."

RAC considers that the epidemiological cohort study (Marez *et al*.,1993) as well as the survey of workers (Röhm GmbH, 1994) exposed to MMA do not provide conclusive evidence either for classification or for non-classification of the substance as a respiratory sensitiser. For example, the information on Röhm (1994) is minimal and based only on a personal communication from one company, without any information on the health questionnaire used, results or description of exposure scenarios and possible risk management measures (e.g. the use of RPEs).

A number of published single case studies as well as information extracted from occupational diseases databases (RNV3P, SWORD, FIOH) provide *ca*. 70 cases in total, covering the period from 1989 to 2017 in at least three different countries and showing similarities with respect to areas of occupation (particularly nail beauticians and dental and medical prosthesis technicians), raise a concern of MMA induced respiratory sensitisation. However, RAC notes that overall, due to medical confidentiality, there was minimal information available for these case reports, and therefore it is not possible to assess them, including whether the patient was indeed sensitised specifically to methyl methacrylate and the reliability of the occupational asthma diagnosis. Most of the published case studies are also lacking in this respect. **Therefore, the opinion of RAC does not rely on these cases.**

RAC considers that the recent cohort study by Suojalehto *et al*. (2020) provides reliable human data showing the potential of MMA to induce respiratory sensitisation, although the number of cases that could be attributed specifically to it was low (n=6). This was a clinical study and not designed for classification purposes. However, RAC considers that it employed the state-of-the art methodology available for diagnostics of occupational asthma due to respiratory sensitisation. Therefore, and considering the CLP criteria, RAC is of the opinion that the study is valid for the purpose of classification. Also the study by Walters *et al*. (2017) supports the conclusion that MMA has respiratory sensitising potential. According to the authors of Suojalehto *et al.* (2020), the patients in these two studies did not overlap. Although the specific link between methyl methacrylate exposure and specific reaction in SIC could be verified in only the cases in Suojalehto *et al*. (2020), it cannot be concluded that such a link does not exist in the rest of the reported cases, where details were lacking.

RAC acknowledges the fact that methyl methacrylate is a respiratory irritant that can provoke asthmatic reactions due to its irritant effects and has an existing harmonised classification as STOT SE 3; H335. Moreover, with the currently available information, it is not possible to identify the mechanism leading to asthma. RAC takes into account that there are no immunological tests available to robustly demonstrate respiratory sensitisation caused by methyl methacrylate, because low molecular weight molecules do not act via an IgE dependent mechanism. According to CLP provisions, "*immunological mechanisms do not have to be demonstrated*" in order to classify a substance as respiratory sensitiser.

In addition, the difference between an irritating mechanism and sensitisation can be difficult to define with respect to clinical symptoms. However, generally a latency between the first exposure and the occurrence of the symptoms indicates more in favour of a sensitisation. Also, the positive

reactions in the placebo controlled SICs strongly argue for a mechanism based on respiratory sensitisation (Suojalehto *et al*., 2020).

The prevalence of asthma cases in the MMA exposed population is unknown. As a consequence, sub-categorisation into Resp. Sens. 1A or 1B is not possible. It should also be noted that overall, it is possible that MMA induced occupational asthma cases are underdiagnosed and underreported. As MMA is not classified as a respiratory sensitiser, physicians are generally unlikely to suspect it as a causative agent behind (occupational) asthma cases). It is also possible that particular exposure conditions, not applicable to all uses, play a role. Finally, according to the CLP, the results of positive specific bronchial challenge tests are considered to provide sufficient evidence for classification on their own.

In conclusion, RAC agrees with the classification proposed by the DS as **Resp. Sens. 1; H334** based on evidence in humans for methyl methacrylate. The available data do not allow for sub-categorisation.

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ANNEXES:

Annex 1 Summary table of human data on respiratory sensitisation from RNV3P, SWORD, FIOH databases

Annex 2 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 3 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).

Annex 4: Records of the targeted consultation following the submission of a study relating to the classification for respiratory sensitisation

Annex 5: Response from Suojalehto *et al*. to ECHA request D(2021)0116

Annex 1

Summary table of human data on respiratory sensitisation from RNV3P, SWORD, FIOH databases

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Case report #1	MMA	Woman (26-year old) working as nail technician.	Occupational disease: allergic occupational asthma. Needed an professional reconversion. High level of attributability	RNV3P database
Case report #2	MMA	Woman (30-year old) working as nail	Occupational disease: occupational allergic asthma	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		technician.	High level of attributability	
Case report #3	MMA	Man (44-year old) working as dental technician.	Occupational disease: occupational asthma High level of attributability	RNV3P database
Case report #4	MMA	Man (58-year old) working in public administration	Occupational disease: predominantly allergic asthma due to an exposure to MMA. Pleural plaques observed following a scanner examination High level of attributability	RNV3P database
Case report #5	MMA	Man (35-year old) working as dental technician	Occupational disease: severe occupational asthma because of MMA exposure High level of attributability	RNV3P database
Case report #6	MMA	Man (57-year old) working as dental technician.	Occupational disease: Allergic occupational asthma High level of attributability	RNV3P database
Case report #7	MMA	Man (48-year old) working in car industry	Occupational disease: predominantly allergic asthma and rhinitis proved using functional respiratory investigations. High level of attributability	RNV3P database
Case report #8	MMA	Man (29-year old) exposed to UV inks composed of MMA	Occupational disease: asthma High level of attributability	RNV3P database
Case report #9	MMA	Woman (51-year old) working as dental assistant.	Occupational disease: asthma High level of attributability	RNV3P database
Case report #10	MMA	Man (27-year old) working as road painter.	Occupational disease: Increase in the frequency of asthma crisis following exposure to special paints designed for roads and which contain MMA High level of attributability	RNV3P database
Case report #11	MMA	Man (43-year old) working as dental technician.	Occupational disease: occupational asthma for 30 years with FEV1 (Forced expiratory volume in one second) of 1.6L. No silicosis but respiratory function worsening with a major post tabacco emphysema High level of attributability	RNV3P database
Case report #12	MMA	Woman (31-year old) working as nail technician.	Occupational disease: occupational asthma High level of attributability	RNV3P database
Case report #13	MMA	Woman (38-year old) formely working as nail manufacturer.	Occupational disease: typical occupational asthma with sequelae from her previous job. Forced to change her job.	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			High level of attributability	
Case report #14	MMA	Man (54-year old) working as silkscreen designer.	Occupational disease: predominantly allergic asthma due to an exposure to MMA. High level of attributability	RNV3P database
Case report #15	MMA	Woman (53-year old) working as moulder technician in a beach umbrella factory.	Occupational disease: predominantly allergic asthma due to an exposure to resins. High level of attributability	RNV3P database
Case report #16	MMA	Man (36-year old) working as dental technician.	Occupational disease: predominantly allergic occupational asthma due to resins handling. High level of attributability	RNV3P database
Case report #17	MMA	Man (50-year old) working as dental technician.	Occupational disease: non allergic occupational asthma High level of attributability	RNV3P database
Case report #18	MMA	Man (39-year old) working as construction electrician.	Occupational disease: asthma. High level of attributability	RNV3P database
Case report #19	MMA	Woman (23-year old) working as a professional nail prothesist.	Occupational disease: allergic rhinitis. Asthma due to an exposure to MMA. high level of attributability	RNV3P database
Case report #20	MMA	Woman (40-year old) working as a professional nail prothesist.	Occupational disease: occupational asthma. High level of attributability	RNV3P database
Case report #21	MMA	Woman (44-year old) working as dental technician.	Occupational disease: asthma and eczema following an exposure to MMA. High level of attributability	RNV3P database
Case report #22	MMA	Man (58-year old) working as dental technician.	Occupational disease: asthma following an exposure to MMA. High level of attributability	RNV3P database
Case report #23	MMA	Woman (22-year old) working as nail technician.	Occupational disease: occupational asthma Moderate level of attributability	RNV3P database
Case report #24	MMA	Man (25-year old) working as dental technician	Occupational disease: occupational asthma because of MMA exposure Moderate level of attributability	RNV3P database
Case report #25	MMA	Woman (50-year old) working as dental technician	Occupational disease: asthma Moderate level of attributability	RNV3P database
Case report #26	MMA	Man (62-year old) working as carpenter	Occupational disease: asthma which led to disability	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
			Moderate level of attributability	
Case report #27	MMA	Man (30-year old) working in furniture industry exposed to MMA	Occupational disease: asthma. Breathing difficulties due to occupational exposure. Moderate level of attributability	RNV3P database
Case report #28	MMA	Man (51-year old) working as machine operator in polystyrene industry.	Occupational disease: respiratory symptoms, asthma. Moderate level of attributability	RNV3P database
Case report #29	MMA	Woman (46-year old) working as machine operator in polystyrene industry.	Occupational disease: asthma Moderate level of attributability	RNV3P database
Case report #30	MMA	Men (49-year old) packer in polystyrene industry.	Occupational disease: asthma Moderate level of attributability	RNV3P database
Case report #31	MMA	Man (32-year old) working in manufacturing medical instruments industry.	Occupational disease: asthma following exposure to powders containing MMA Moderate level of attributability	RNV3P database
Case report #32	MMA	Man (57-year old) working as painter-decorator on glass or ceramic.	Occupational disease: predominantly allergic asthma. Moderate level of attributability	RNV3P database
Case report #33	MMA	Woman (45-year old) working as dental technician.	Occupational disease: asthma aggravated by MMA and dust. Moderate level of attributability	RNV3P database
Case report #34	MMA	Man (63-year old) working as house painter.	Occupational disease: asthma. Moderate level of attributability	RNV3P database
Case report #35	MMA	Man (38-year old) working as house painter.	Occupational disease: asthma, rhinitis because of MMA handling. If still exposed to MMA, will need to change his job Moderate level of attributability	RNV3P database
Case report #36	MMA	Man (48-year old) working as dental technician.	Occupational disease: possible occupational asthma. Moderate level of attributability	RNV3P database
Case report #37	MMA	Man (49-year old) working as dental technician.	Occupational disease: asthma. Moderate level of attributability	RNV3P database
Case report #38	MMA	Woman (23-year old) working as nail technician.	Occupational disease: asthma and rhinitis. Moderate level of attributability	RNV3P database
Case report #39	MMA	Woman (39-year old) working as nail	Occupational disease: asthma High level of attributability	RNV3P database

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
		technician.		
Case report #40	MMA	Woman (31-year old)	Occupational disease: asthma Moderate level of attributability	RNV3P database
Case report #41	MMA	Woman (29-year old) working as dental technician.	Occupational disease: asthma High level of attributability	RNV3P database
Case report #42	MMA	Woman (50-year old) working in automotive industry	Occupational disease: asthma High level of attributability	RNV3P database
Case report #43	MMA	Man (48-year old) working in furniture industry	Occupational disease: asthma proved by a very positive reversibility test High level of attributability	RNV3P database
23 actual cases : Cases #44-66	MMA	61% men working in various sectors	Occupational disease: asthma reported by chest physicians No information on attributability	SWORD database
Case #67	MMA	Man working in the manufacture of medical devices	Occupational disease: asthma Reported by occupational physicians No information on attributability	OPRA database
Case #68	MMA	Dentist has worked with dental primers, adhesives and fillers; prosthetic methacrylate liquid and powder during 15 years before asthma symptoms	Occupational disease: asthma with a late reaction in specific inhalation challenges (SIC) after 1-8 hour after exposure. No information on attributability	FIOH database
Case #69	MMA	Dentist working with prosthetic material. Has worked during 5 years before asthma symptoms	Occupational disease: asthma with a late reaction in specific inhalation challenges (SIC) meaning after 1-8 hour after exposure. No information on attributability	FIOH database
Case #70	MMA	Dental technician working with prosthetic material. Has worked for 23 years before asthma symptoms	Occupational disease: asthma with dual reaction in specific inhalation challenges (SIC) meaning both early and late reactions No information on attributability	FIOH database
Case #71	MMA	Production worker working with 2-component lamination resin. Has worked during 1 years before asthma symptoms	Occupational disease: asthma with an early reaction in specific inhalation challenges (SIC) meaning within 1 hour after exposure. No information on attributability	FIOH database