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Comments on the dossier proposing harmonised classification
and labelling of Methyl Methacrylate

Dear Sir or Madam,

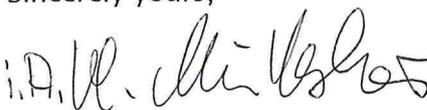
On May 6, 2019 ECHA has published an CLH proposal of the
French MSCA to classify Methyl Methacrylate, CAS number 80-62-
6, for its potential Respiratory Sensitization properties (H334).

We are herewith commenting on behalf of Evonik Röhm GmbH as
Lead Registrant of this substance and also on behalf of the
supporting Methacrylate REACH Task Force.

We do not agree with the CLH proposal for the reasons presented
in the attached comment and, instead, we propose that the
current Annex VI entry remains unchanged.

Thank you in advance for your comprehensive considerations of
our assessment provided below.

Sincerely yours,



i.A. Dr. Harald Müllerschön
Director Hazard and Risk Management
Product Stewardship



i.A. Dr. Knut Kreuzer
Toxicologist (certified)
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Attachment

Comment on the CLH report proposing harmonised classification
and labelling of Methyl Methacrylate (MMA), July 5, 2019

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Comment on the CLH report proposing harmonised classification and labelling of Methyl Methacrylate (MMA)

Substance name: methyl methacrylate (MMA)

CAS Number: 80-62-6

EC Number: 201-297-1

Hazard class open for commenting: Respiratory Sensitisation (H334)

Commenting Party:

Evonik Röhm GmbH (Lead Registrant of MMA)

on behalf of the Methacrylate REACH Task Force

Technical input provided by

Dr. Ian Kimber, Kimber Biomedical Ltd.; and

Dr. Frank Gerberick, GF3 Consultancy LLC

Date: July 5, 2019

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2 Summary

The CLH report proposes that Methyl Methacrylate (MMA) should be classified as Respiratory Sensitizer, Cat. 1 H334 according to CLP Regulation and based on human data. We take the opportunity to comment on both the quality of the CLH proposal and also on the proposed additional classification itself.

An CLH proposal “*must contain sufficient information to allow an independent assessment*” according to ECHA. However, the weight-of-evidence (WoE) approach within this CLH report lacks fundamental scientific standards as defined by ECHA and the European Scientific Committee SCHEER. For example, the review of publicly available literature detected fundamental deficiencies in the coding schemes of the RNV3P database and the likelihood of the exposure of a patient to MMA as causative agent for the respective diagnosis (the so called “attributability”) has not been sufficiently checked for plausibility. As a consequence, 54 of in total 79 cases in the CLH report were either not attributable to MMA as MMA was not used in the respective job sectors, or co-exposure to other chemicals was highly likely and may have been the cause of the health effect reported.

Thus, and seen on its own, the disregard of these standards results in a misinterpretation of the weak evidence that the approach does present and does not take into account conflicting evidence of higher reliability from other publicly available sources. Thus, the WoE approach of the CLH proposal is not balanced and not scientifically justified.

The lack of fundamental understanding is also true for endpoint specific aspects. For respiratory sensitisation, evidence for a biphasic mode of action with an initial induction phase followed by an elicitation phase has to be provided so that the human data allow for the determination of “causation” of the development of asthma and not simply that it “provokes” or “aggravates” a pre-existing condition. As a further consequence, this CLH proposal does not allow to clearly distinguish between respiratory irritation effects (for which MMA is already classified) against the respiratory sensitisation effects claimed in the CLH proposal. Therefore, a fundamental piece of information for a valid WoE approach for the respiratory sensitisation potential of MMA is missing.

In contrast, the assessment that we have made in the limited time available and that refers to a broader database than the CLH report complies to the above mentioned standards of ECHA and SCHEER. The respective WoE approach more than adequately demonstrates a lack of confidence in the CLH proposal that MMA is a causative agent for occupational asthma.

Instead, all available evidence reviewed in the literature confirm with sufficient evidence that MMA has the potential to provoke respiratory irritation in pre-existing asthma cases. As such, there is sufficient doubt in the strength of evidence supporting classification of MMA as respiratory sensitiser.

As a consequence, we do not agree to the CLH proposal and, instead, we propose that the current Annex VI entry remains unchanged.

3 Respiratory Sensitisation/ Occupational Asthma

3.1 Regulatory requirements

3.1.1 CLP (Regulation on classification, labelling and packaging of substances)

3.1.1.1 *Biphasic mode of action not considered*

CLP defines a respiratory sensitiser as “*a substance that will lead to hypersensitivity of the airways following inhalation of the substance*” (EU, 2008). Sensitisation is always linked with an initial induction phase followed by an elicitation phase which is clearly different from a respiratory irritative effect (see CLP chapter 3.4.1.3 and the box in chapter 3.2.1). In other words: when it is a CLP requirement to demonstrate “*evidence in humans that the substance can lead to specific respiratory hypersensitivity*” it must be clear that **specific evidence** has to be provided that the human data allow for the determination of “causation” of the development of asthma and not simply that it “provokes” or “aggravates” a pre-existing condition. **This important detail of the strength of the evidence supporting causation of asthma in each case study cited is not addressed in the report. Therefore, a fundamental piece of information for a valid WoE approach for the respiratory sensitisation potential of MMA is missing.**

We believe that the statement in the CLH report chapter 10.6.2 that for a respiratory irritant like MMA it is difficult to distinguish between asthmagenic (= inducing asthma) and non-asthmagenic (irritant, provoking asthma) effects is indeed often the case. But this argument should not be used to justify an oversimplification of a recognised complex etiology. This is inappropriate and misleading.

We would like to outline at this point that our assessment provided in this document considers this aspect and comes to the conclusion that there is no convincing evidence that MMA is a respiratory sensitiser or causes asthma.

3.1.1.2 *Further aspects which were not considered*

The argumentation line of the CLH report is solely based on human evidence, which is typical for this endpoint. Here, a fundamental CLP requirement “*for a decision on classification to take into account, in addition to the evidence from the cases “(is)”: (a) the size of the population exposed; (b) the extent of exposure.*”

In the CLH report, the **size of the exposed population** for the job sectors of interest is not mentioned for any of these sectors. Consequently, a key piece of information for the decision is not available from the report. The report authors themselves confirmed this limitation in their statement on subcategorization (“... *there is no adequate information on the level of exposure mentioned in the case reports and the frequency of this pathology*”).

In contrast, within the short timeframe of public consultation we were able to collect relevant information for the most relevant job sector (i.e., dental) mentioned in the national occupational health databases, hereby focusing on the situation in France as example. This sector-specific information on the calculated prevalence must be set in relation to the overall prevalence of bronchial asthma in Western Europe, being 5-10% of the total population with a strong tendency to

increase (WHO, 2019). This proportion can be understood as a pool of generally respiratory hypersensitive individuals. From this perspective, the several magnitudes lower prevalence for potential occupational asthma in the dental sector does not support any additional hazard or risk concern for MMA. Instead, the data can be interpreted in a way that the presented RNV3P cases just display a subset of this pool of generally respiratory hypersensitive individuals. This is of particular importance given that MMA is an irritant chemical and a wider range of stimuli including cold air, exercise and irritant chemicals have been shown to aggravate preexisting asthma conditions.

The **extent of exposure** is another relevant piece of information for the decision on classification. For the majority of presented cases, namely that in the national databases, this information is not directly available in the report. Furthermore, since such information is extremely scarce or, in most cases, absent in the public literature this precludes a valid assessment of the contribution of the extent of exposure. The same is true for the clinical history of patients, where key data on the medical condition of the individual is typically lacking. Both the extent of exposure and the clinical history are extremely important in establishing the basis for associating exposure to MMA and causation i.e. development of asthma. Furthermore, in the case of the RNV3P database, occupational professionals have offered a general contradiction by indicating that some clinical cases classified as attributed to MMA were actually associated with substances other than MMA (p8 ANSES, 2017). This clearly points to the unreliable nature of some of cited cases and as such calls into question the robustness of the analysis done by ANSES.

As part of our alternative WoE approach, a brief information on cohort sizes and exposure concentrations is provided in Appendix 9.3.

3.1.2 Endpoint specific Guidance R7.a

3.1.2.1 *Asthma-like symptoms induced by irritants do not trigger classification for respiratory sensitisation*

The CLH report states that *“Additionally according to CLP “the condition will have the clinical character of an allergic reaction”, which is the case for methyl methacrylate and “immunological mechanisms do not have to be demonstrated” to classify the substance as a respiratory sensitiser”.*

In this regard, ECHA’s endpoint specific guidance (2017) attest to an uncertainty regarding the exact mechanisms leading to respiratory sensitisation, but goes on to state that it is very clear that misinterpretation and wrong classification is not warranted: ***“In case there is evidence available that the substance induces asthma-like symptoms by irritation only, these substances should not be considered as respiratory sensitisers”.***

It is apparent that the CLH report underestimates the significance of properly evaluating the confounding nature of irritation when evaluating case reports of asthma and consequently contains no scientifically valid assessment allowing the distinction between asthmagenic and non-asthmagenic effects in the presented cases. As a consequence, there is no evidence provided in the CLH report that MMA is a cause of asthma - either immunological (allergic asthma) or non-immunological (see chapter 3.2 for further details).

3.1.2.2 Quality criteria for human data is not fulfilled

ECHA's endpoint specific guidance (2017) sets out criteria for information requirements for human data on this endpoint as follows:

- “- the test protocol used (study design, controls);*
- the substance or preparation studied (should be the main, and ideally, the only substance or preparation present which may possess the hazard under investigation);*
- the extent of exposure (magnitude, frequency and duration);*
- the frequency of effects (versus number of persons exposed);*
- the persistence or absence of health effects (objective description and evaluation);*
- the presence of confounding factors (e.g. pre-existing respiratory health effects, medication; presence of other respiratory sensitisers);*
- the relevance with respect to the group size, statistics, documentation;*
- the healthy worker effect.”*

This level of information is missing for all mentioned cases from the national occupational health databases cited in the CLH report – representing the vast majority of presented cases in the report. Furthermore, for other publications cited no assessment was made as to the conformity of the available data against these criteria making it impossible to make scientifically valid conclusions based upon these cases.

3.1.2.3 Medical surveillance reports underweighed

ECHA's endpoint specific guidance (2017) also provided insights on ECHA's position on the relative weight that should be attributed to medical surveillance reports demonstrating a lack of indication of development of respiratory allergy, or related symptoms, after regular significant inhalation exposure to a substance for a sustained period of time. In this regard, the cross-sectional worker health study report of Röhms (1994) provides valuable evidence supporting an absence of concern for respiratory sensitisation hazard in MMA-exposed workers. Such evidence appears to be disregarded in the CLH report but should be given greater weight if a sound weight-of-evidence approach were to be applied.

3.1.3 ECHA and EU/COM/ SCHEER guidance on use of Weight-of-Evidence

The CLH report cites 71 cases of occupational asthma from the national occupational health databases with the French RNV3P database as main source as well as several publications and concludes that *“it appeared necessary to classify the substance as a respiratory sensitiser”*. This justification infers a weight-of-evidence assessment conclusion since no case study, or studies, were cited as being of sufficient strength alone to justify classification.

ECHA describes that the use of WoE approaches in hazard is beneficial when *a) the information from a single piece of evidence alone is not sufficient to fulfil an information requirement. This could be, for example, due to clear deficiencies in one of the existing studies, and b) when individual studies provide different or conflicting conclusions*. In the case of the CLH proposal for MMA and respiratory sensitisation the available data satisfied both criteria so use of WoE is justified.

ECHA goes on to state that *“The weight you should give to the available evidence depends on factors such as the quality of the data, consistency of results, nature and severity of effects, and relevance of the information. The weight-of-evidence approach requires use of scientific judgment and, therefore, it is essential to provide adequate and reliable documentation”*. Indeed, ECHA even provides a

template for weight-of-evidence / uncertainty in hazard assessment in which it describes the following steps:

- 1) Collection and documentation of all information - Documentation of search strategy & documentation/reporting of evidence,
- 2) Assessment of quality of individual evidence,
- 3) Integration & Weighing of evidence (WoE analysis) - Application of Levels of Confidence,
- 4) Uncertainty Analysis, and
- 5) Conclusions

This overall process is consistent with the Memorandum on WoE and uncertainties published by the European Commission and its Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) in June 2018 (EU SCHEER 2018). The guidance documents identify several key steps that should be followed.

Firstly, Assessing the quality of individual lines of evidence. SCHEER's document identifies this as being a major task involving the assessment of the individual lines of evidence to judge their validity, reliability and relevance (Klimisch et al., 1997; Nendza et al., 2010; ECHA, 2010). They identify aspects of:

- a. Relevance: This defines whether a set of data (e.g. from a publication) is appropriate for a particular hazard identification or risk characterisation and therefore has the potential to contribute to answering the respective questions.
- b. Validity: Evaluating the method used for the generation of data for a specific endpoint relative to accepted guidelines. Or: Evaluating the model used for the generation of data against validation principles such as the OECD validation principles.
- c. Reliability: Evaluating an individual result with regard to the inherent quality of a test report or publication relating to a, preferably standardised, methodology and the way that the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings.

Key issues further identified requiring evaluation were i) Characterisation of the stressor, ii) Soundness and appropriateness of the methodology and models, iii) Extent to which the full details of methodology are provided, iv) Reproducibility of findings between experiments/observations, and v) Relevance of a set of data for a particular endpoint.

In regard to the assessment and weighing of individual lines of evidence, critically the CLH documentation fails to meet the standards proposed by ECHA/ SCHEER at many levels.

- 1) Notwithstanding the fact that the RNV3P database contains specific limitations (which are discussed in chapter 5.1) the data cited provides no detail as to the methods employed, the critical findings or any give evidence of the clarity and plausibility of the findings. As such they are not transparent and cannot be assigned a rating for relevance, validity or reliability and according to the scheme introduced by Klimisch et al. (1997) would be assessed with a score of 4 ("not assignable").
- 2) Considering the likelihood for co-exposure to other irritant/sensitising chemicals in the industry sectors identified as being the source of these claimed cases of asthma the absence of even basic information on historical workplace exposures leaves the judgement of causality to be based solely upon patient's claims of workplace pattern of effects. This is

unavoidably open to elaboration or bias considering many of these patients were seeking claims for workplace related disease.

- 3) Considering that MMA is recognised as an irritant chemical, the absence of controlled provocation challenge studies renders the diagnosis unreliable, makes the judgement of causality open to error.
- 4) The causal association between “development” of asthma and exposure to MMA by clinicians appears in the majority of cited cases to be based upon an undocumented work history and self-reported claims of use of MMA, combined with a general recognition of the use of “acrylates” in those industries without any attempt to determine if MMA was indeed involved. Making a causal association even more difficult to evaluate is the fact that professionals openly acknowledge that the RNV3P reference code to MMA was used for other methacrylates and acrylates. In several cases we investigated MMA was not used and other chemicals can readily be identified as potentially being the causation of the observed asthma.
- 5) Several papers cited are secondary literature and the authors have failed to go back to the primary literature to ascertain relevance, validity and reliability thereby inferring a high prevalence of cases of asthma caused by MMA.

In regard to this last point, the CLH proposal presents an argument that justifies classification based upon a WoE of cases of asthma caused by MMA relying upon a) that the individual lines of evidence are strong whereas the evidence would suggest otherwise and b) the number of supposed cases is high indicating a high prevalence, without making any efforts to document the actual level of employment in these sectors which would give a true reflection of actual prevalence. The overall impression being presented is that there are many cases of proven asthma caused by MMA whereas thorough analysis of the available human data indicates to the contrary.

In contrast, to the approach taken in the CLH proposal, SCHEER proposed a system that classifies results of analysis for human and environmental risks in terms of:

- 1) Strong weight of evidence: Coherent evidence from a primary line of evidence (human, animal, environment) and one or more other lines of evidence (in particular mode/mechanistic studies) in the absence of conflicting evidence from one of the other lines of evidence (no important data gaps).
- 2) Moderate weight of evidence: good evidence from a primary line of evidence but evidence from several other lines is missing (important data gaps).
- 3) Weak weight of evidence: weak evidence from the primary lines of evidence (severe data gaps).
- 4) Uncertain weight of evidence: due to conflicting information from different lines of evidence that cannot be explained in scientific terms.
- 5) Weighing of evidence not possible: No suitable evidence available.

If the approach recommended by SCHEER were to be applied to the available data cited in the CLH proposal then this would lead, at best, to an overall conclusion that there is “weak evidence” that is insufficient to justify classification of MMA as a respiratory sensitiser since not one study identified could be regarded as “good evidence of high reliability” and there is available conflicting evidence indicating that MMA does not cause asthma.

3.2 Chemical respiratory allergy and non-allergic asthmagens/irritants

3.2.1 Chemical-induced asthma: definitions and the question of causation

Asthma is a chronic inflammatory disease of the airways characterised by airway obstruction, wheezing, and readily triggered bronchospasm. Chemical-induced asthma is an important occupational health problem (Kimber et al., 2011).

The pathogenesis of asthma can be allergic or non-allergic. By definition, allergic asthma requires the stimulation of a specific immune response (see box below), whereas non-allergic asthma is independent of adaptive immune function.

Allergy/allergic disease develops in 2 phases. In the first phase, exposure of a susceptible subject to the inducing allergen stimulates immunological priming termed sensitisation. The second phase occurs when the sensitised individual encounters the same allergen, via a relevant route of exposure, for a second time. An accelerated and more aggressive secondary immune response is mounted and this, in turn, results in the elicitation of an inflammatory reaction recognised clinically as allergic disease.

True chemical respiratory allergy follows the pattern outlined in the definition above, and is dependent upon priming of the immune system that causes allergic sensitisation of the respiratory tract. Sensitisation is specific for a particular chemical allergen (or structurally closely related chemical allergens). If that sensitised subject is exposed subsequently by inhalation to the inducing allergen then an accelerated and exaggerated immune response will be elicited in the respiratory tract that results in a respiratory allergic reaction characterised by rhinitis and/or asthma (Kimber et al., 2011).

In contrast, non-allergic asthmagens can cause similar adverse health effects, but without stimulation of an adaptive immune response.

The guidance provided by the European Chemicals Agency (ECHA) for the implementation of REACH states that a respiratory sensitiser is defined *“as an agent that will lead to hypersensitivity of the airways following inhalation exposure of that agent”*. The Guidance also indicates that: *“Respiratory sensitisation (or hypersensitivity) is a term that is used to describe asthma and other related respiratory conditions (rhinitis, extrinsic allergic alveolitis), irrespective of the mechanism (immunological or non-immunological) by which they are caused”* (see chapter 3.1.1).

The difficulty is that this definition and guidance embraces 2 very different types of chemical toxicants: (a) true chemical respiratory allergens that induce asthma through immunological mechanisms, and (b) chemicals that induce asthma via respiratory irritation (with which adverse health effects are caused by non-immunological mechanisms).

This is not a new issue. The problems caused by grouping together chemicals that cause similar adverse health effects in the respiratory tract, but by different mechanisms, has been discussed previously (Kimber et al., 2001).

Non-allergic asthma, usually provoked by inhalation exposure to irritants does not require, and is not associated with, an adaptive immune response. Such occupational asthma usually develops with time in response to moderate levels of exposure to irritants.

However, one important subset of non-allergic asthma is the Reactive Airways Dysfunction Syndrome (RADS), or acute-onset irritant-induced asthma. RADS is associated characteristically with a single high level respiratory exposure incident to an irritant material that results in rapid onset respiratory symptoms and bronchial hyperreactivity. This airways hyperreactivity commonly persists for some time (Brooks et al., 1985; Alberts and Brooks, 1996; Lau and Tarlo, 2019).

The key point to appreciate is that in subjects with RADS, or in those that have acquired bronchial hyperreactivity via some other cause, exposure to irritant stimuli including irritant chemicals, cold air, exercise, smoke etc. may elicit respiratory reactions. In such instances the irritant chemicals that elicit reactions are not necessarily those that caused the acquisition of hyperreactivity in the first place. It is important, therefore, in the context of causation, to distinguish clearly between those exposures that are able to induce asthma, and those that simply elicit reactions in those that are already hyperreactive (either as the consequence of previous inhalation exposure in the workplace to another unrelated chemical, or due to pre-existing asthma that was acquired independently of the workplace environment).

To summarise, therefore, respiratory reactions to inhaled chemicals embraces the following scenarios/causations:

- Allergic asthma (induced by respiratory sensitising chemicals; such as for instance diisocyanates and acid anhydrides; Kimber et al., 2011).
- Non-allergic asthma associated commonly with respiratory irritants (such as, for instance, cases where chronic workplace inhalation exposure, at moderate levels, to certain cleaning materials has been shown to cause bronchial inflammation and subsequent asthma) (Zock et al., 2001; Evans et al., 2008; Lau and Tarlo, 2019). In addition, non-allergic asthma includes RADS, where a single high level exposure to a respiratory irritant (commonly associated with an accident or spillage) can result in bronchial hyperreactivity (Brooks et al., 1985; Alberts and Brooks, 1996; Lau and Tarlo, 2019).
- Work-exacerbated asthma which is defined as pre-existing asthma that is made worse by workplace exposures (Lau and Tarlo, 2019).

3.2.2 Why is it important to distinguish between different forms of chemical-induced occupational asthma?

There are a number of further reasons why it is important to understand the mechanisms through which occupational asthma has been acquired

- An understanding of whether asthma has been induced through allergic sensitisation, or via alternative mechanisms influences subsequent clinical management (Lau and Tarlo, 2019).
- Allergic sensitisation of the respiratory tract to chemicals can be induced by skin exposure. Subsequent elicitation of an allergic reaction in the respiratory tract will require inhalation exposure to the causative allergen, but immunological priming can occur via skin contact (Kimber, 1996; Kimber et al., 2011). Respiratory reactions to irritants will not be provoked by skin exposure. As a consequence, effective risk management of respiratory allergy must consider carefully, and eliminate, opportunities for skin exposure.
- Repeated exposure to a chemical allergen will likely cause increasing sensitivity to the inducing allergen, and this will be associated with a reduction in the level (threshold) of inhalation

exposure that will be required to elicit an allergic reaction/asthma (Cochrane et al., 2015). It is not clear whether reactions to irritants necessarily become more severe with continued exposure.

- Sensitisation to one chemical allergen can sometimes confer collateral sensitisation to a second, structurally similar, allergen that is immunologically cross-reactive. This is clearly not a consideration with non-allergic asthma.
- For regulatory purpose, and for effective occupational health management, it is necessary to distinguish carefully between those chemicals that have the potential to induce asthma (whether allergic or non-allergic), and those chemicals that do not induce asthma but that can nevertheless elicit respiratory reactions in subjects that already have asthma, or bronchial hyperreactivity associated with – for instance – with RADS.

However, the approaches used for the diagnosis and characterisation of occupational asthma are commonly difficult to interpret. This is a particular problem when judgements are based solely on poorly designed and/or controlled case studies and bronchial provocation tests. Common problems associated with the interpretation of such case studies include the following:

- Inadequate information about the conditions of workplace exposure, and the opportunity for concurrent exposure to a mixture of chemicals, including respiratory irritants
- Lack of information about the latency of reactions (early onset or late onset)
- The use of inappropriately high concentrations for the conduct of inhalation challenges
- Inadequate information relating to the purity of materials used for inhalation challenges

For these reasons, chemicals may be implicated incorrectly as being respiratory sensitisers/causes of occupational asthma. It is essential, therefore, that in reaching decisions about causality and probable mechanism of action, the information available from clinical history, the nature, duration and characteristics of workplace exposure, and bronchial provocation tests, are considered carefully. Importantly, it is necessary to appreciate the limitations of reaching decisions based on case studies and challenge tests.

The absence of such information for all cases cited from the RNV3P database as well as many of the available publications makes it at best uncertain, but typically impossible, to conclude the type of asthma i.e. allergic or non-allergic, and in the case of non-allergic asthma, whether it is caused or just exacerbated by the implicated chemical.

4 Relevant hazard profile of Methyl Methacrylate

4.1 Sensitisation

4.1.1 Respiratory Sensitisation

MMA is currently not classified as respiratory sensitiser. There is no data in experimental animals indicating respiratory sensitisation. MMA is a weak electrophile and consequently is a skin sensitiser of weak potency. Due to its volatility, QSARs predict MMA to be a potential respiratory sensitiser.

The human data in the scientific literature was comprehensively reviewed by the EU-RA (ECB, 2002), SCOEL (2005) and Borak et al. (2011) and consistently came to the conclusion that MMA is not a respiratory sensitiser but was a respiratory irritant (see chapter 6 for more details). No significant new data has been published since these dates that justifies changing this conclusion.

4.1.2 Skin Sensitisation

The current classification for MMA is Cat 1/ H317. The CLH report summarizes correctly the total set of available information on this endpoint “*that methyl methacrylate has to be considered as **weak skin sensitiser***” in report chapter 10.7.1. This is also in line with reliable publications (e.g., Borak et al. 2011; Betts et al. 2006). Based on a scientifically valid WoE approach, MMA is considered to fulfil the CLP criteria for subcategory 1B with respect to both human data (CLP table 3.4.2) and animal data (CLP table 3.4.4; EU, 2008) so that a subcategorization would improve the accuracy of the existing classification.

We, however, understand that it is not foreseen in the public consultation phase of a harmonised classification and labelling activity to propose other classification changes than to the open hazard classes specified by the report submitter. Thus, we will consider a respective separate proposal for harmonized classification at a later time.

Nevertheless it is an important piece of information for the assessment of its respiratory sensitisation potential to know that MMA has a weak potential for skin sensitisation.

4.2 Irritation

4.2.1 Skin irritation

The current classification for MMA is Cat. 2/ H315. The background for the current harmonized classification is a decision of the EU C&L work group in 2001 to classify based on a study in humans where skin reactions had been observed after 48h exposure under occlusive conditions while MMA is not irritating in guideline tests in rabbits. While the decision in favour of the current harmonized classification is clearly a precautionary approach, the data indicate that MMA has a weak potential for irritation of the skin.

4.2.2 Respiratory irritation

The current classification for MMA is STOT SE Cat 3/ H335. Reversible respiratory irritation has been observed after short-term peak exposures to humans at concentration levels exceeding 100 ppm. No influence on olfactory function was reported in a cross-sectional smell test in workers exposed to MMA up to 50 ppm (8 h TWA) and up to 100 ppm in the past (Röhm 1995, Muttray et al. 1997). No effects were seen after single exposures to 50 ppm in a study with human volunteers investigating subclinical, irritating effects (Muttray et al. 2007).

Thus, this current harmonized classification is justified but is important to know that MMA has a relatively weak potential for irritation of the respiratory tract which would only be relevant at workplace concentrations well above the OEL.

4.3 Summary on the hazard profile

MMA is a recognized skin sensitizer of weak potency with a “potential” to be a respiratory sensitizer but there is no evidence that this potential is translated into hazard. It is however a known irritant chemical that is recognized as respiratory irritant in humans.

MMA has a vapour pressure of 37 hPa (20°C) and a vapour density of 3.6 (air = 1). On this basis it can be anticipated that if workers handle liquid MMA without adequate ventilation it is possible that vapour concentrations exceeding the current OEL may be formed within the breathing zone. Data submitted under ESR from the Cast PMMA sheet industry and publications such as that by Pickering et al., 1986, in which peak exposures of 374 ppm were measured when handling MMA without ventilation. Whilst in many industry handling MMA routinely are not related to respiratory irritation, it is possible that pre-existing asthmatics may be more sensitive.

Considering that asthma (from whatever cause) and RADS (Reactive Airways Dysfunction Syndrome) are characterised by bronchial hyperresponsiveness it is not surprising that pre-existing asthmatics may be more susceptible to irritation by acute high concentrations of MMA vapour than healthy workers.

As an example, bronchial hyperresponsiveness is routinely measured by bronchial provocation challenge with methacholine. Methacholine is not an asthmagen (that is, it does not cause asthma), but is a non-selective muscarinic receptor agonist that stimulates the parasympathetic nervous system acting directly on bronchial smooth muscle to elicit a respiratory reaction. The greater the extent of previously acquired bronchial hyperresponsiveness, the greater will be responsiveness to methacholine, and the lower the concentration of methacholine required to elicit a reaction (Mauger et al., 2001).

This diagnostic procedure illustrates the widely appreciated fact that those with bronchial hyperresponsiveness are more reactive than normal subjects to a variety of external stimuli, including, for instance, strong smells, wood and cigarette smoke, exercise, cold air and chemical irritants.

The important point is that subjects with pre-existing asthma (irritant or allergic), or with RADS, will display increased responsiveness to airborne irritants, like MMA, in the workplace environment, and will respond to concentrations of such irritants that will not trigger reactions in normal, healthy subjects.

In this way workers may demonstrate a work-related pattern of asthma symptoms because MMA is exacerbating their asthma but this does not mean that MMA necessarily caused the asthma in the first place. As such claims of “developing asthma during work” or “work-related pattern of asthma symptoms” are not sufficiently diagnostic in their own right to provide proof of “causation”. If this were the case then these non-chemical elicitors such as strong smells, wood and cigarette smoke, exercise, cold air would also be classified as asthmagenic.

No indication of irritation-derived hyperreactive airways

Further inhalation data requires specific attention with regard to the CLH proposal as they do not indicate that MMA causes irritation-derived hyperreactive airways.

- Animal data: Particularly in the range finding studies for the NTP carcinogenicity studies by inhalation the rodents were exposed to very high concentrations of MMA (up to 5000 ppm for 14 weeks; NTP, 1986). The most sensitive tissue in the respiratory tract in the NTP studies was olfactory epithelium with a LOEL in female rats of 250 ppm in the 2-year main study. Subsequent studies indicated that this tissue is particularly susceptible, because it has a high activity of carboxylesterases which resulted in histopathological effects due to one of the primary metabolites, methacrylic acid, which is a strong irritant and corrosive. Histopathological changes in the lower respiratory tract, which would be the relevant target for this analysis, have only been found in the range finder with high doses of 2000 ppm and above.
- Human workplace data: In data collections regarding human exposure, exposure levels were far from such concentrations. The most relevant collection of exposure data, particularly before 1990, when OELs were higher than today or absent, is the “Risk Assessment Report on Methyl methacrylate” (EU-RA, ECB 2002). The two areas of use with the highest documented exposure concentrations are reactive floor coating using a reactive coating based on MMA and cast sheet production – a sheet of transparent acrylic is polymerized between two sheets of mineral glass.
 - Reactive floor coating
The EU-RA lists cases where workers had been exposed to up to 100 ppm (8 h TWA and up to 600 ppm for task measurements; Lindbergh et al. 1991). A large cross-sectional study on this group of workers is absent, however, a small group of 10 floorlayers has been investigated in a study by Lindbergh et al. (1991) of the Swedish National Institute of Occupational Health. The medical examination did not find significant health problems. The study included blood and urine analysis, lung function and a neurophysiological and psychophysiological examination. The only finding was that some of the workers reported respiratory irritation.
 - Cast sheet production
The EU-RA documents exposures in this area below the current HBROEL of 50 ppm, but older measurements – before the refinement of the exhaust ventilation equipment, documented higher exposures of up to 100 ppm (8 h TWA and task measurements of up to several 100 ppm). Worker health studies had been initiated including the workers from two cast sheet plants to ensure the health of the workers. Two subsequent investigations with a general medical survey and a lung function test (Röhm 1994) and a functional smell test (Muttray et al., 1997). Both studies included workers with a long work history who had been working in the area

for – on average - 9 years and some for more than 20 years. In both studies work-related health effects were absent.

- Study in human volunteers for subclinical effects (Muttray et al., 2007)
In this study human volunteers had been exposed to MMA at 50 ppm for 4 hours. Before and after the exposure the mucociliar transport time and the odour threshold of n-Butanol were determined, and also after the exposure the concentrations of the interleukins IL-1 β and IL-8 in the nose secretion. There was no evidence of adverse effects of the exposure.

In humans MMA may be irritating to the respiratory tract but primarily at concentrations high above the OEL. Because of this it can be expected that MMA may also have the potential to provoke an asthmatic response in sensitive individuals with a pre-existing asthmatic condition. The existing information of prevalence in Appendix 61 indicates that this sensitive subpopulation is just a very small fraction of all asthmatics expected in the exposed cohort. In cast sheet production and the related worker health studies there was no evidence of work-related asthma.

Interrelation of the hazard potential with the high vapour pressure of MMA

As outlined in the above subchapters, MMA has generally a weak irritating potential; this is also supported by the fact that MMA is not an eye irritant in animal studies (see REACH registration dossier of MMA). On the other hand, MMA has a relatively high vapour pressure of 37 hPa at 20°C. Albeit MMA has a weak irritation potential, a combination of high vapour pressure and unfavourable exposure conditions (insufficient ventilation – or lack thereof) may led to situations where concentrations are reached where respiratory irritant effects can be observed in humans. This is most likely in those occupational areas, where open handling of MMA occurs and exposure control measures are limited. This observation has already been described before in the EU-RA (ECB, 2002).

5 Information on the potential of MMA for occupational asthma provided in the CLH report

The information on the potential of MMA for occupational asthma provided in the CLH report was carefully reviewed and is commented as follows. More relevant, publicly available information on the potential of MMA for occupational asthma is provided in chapter 6. These databases include primarily the French RNV3P but also UK's THOR/SWORD network, and the Finnish FIOH database. More publicly available information on the potential of MMA for occupational asthma is provided in chapter 6.

5.1 The RNV3P database

The main source of the cases used in the CLH report as evidence for the proposed addition of respiratory sensitisation classification for MMA is the French occupational health database RNV3P. The database and its network are well described in chapter 10.6.1 of the CLH report. This network is a useful program for the exchange of occupational health information with its all the mentioned implications like the generation of alerts for preventive actions, also for specific job sectors.

It is important to note that critical information within the database is not publicly available, therefore much effort has been made to conduct a valid assessment of the reliability of this information source. Several aspects of RNV3P have been identified which challenge this database's validity as a useable information source for the assessment of MMA as an asthmagenic substance, namely: diagnosis errors, reporting bias, and a flawed relationship of the diagnosis to MMA exposure.

5.1.1 Diagnosis errors

Florentin and his coworkers from several French medical faculties (2017) investigated job-exposure matrices for exposure assessments in occupational safety and health monitoring systems. They came to the general conclusion that even in the RNV3P network of physicians "*errors in diagnosis are possible*".

More focused to potentially asthma-related diagnosis, Paris et al. (2012) stated that "*persistent discrepancies are observed concerning the diagnosis of OA ("occupational asthma") by clinicians. Consequently, differences in diagnostic procedures may exist between centres both for OA and WRA ("work-related asthma"). Moreover, the absence of specific challenge test procedures in most centres prevented us from distinguishing between WEA ("work-exacerbated asthma") and OA with a reasonable level of confidence.*" These comments should not be readily discounted as the publication was co-written by members of RNV3P who have direct and detailed insight into the network than provided in the CLH report.

We can contribute to this statement with following information: Based on scientific expertise, we would expect the reactive airway dysfunction syndrome (RADS) as a likely and correct diagnosis for high-level exposure to MMA (see chapter 3.2). RADS as diagnosis however has been introduced into the ICD-10 scheme just recently in 2015 while the diagnosis for asthma exists since the introduction of ICD-10. In other words, before 2015 physicians had no opportunity to diagnose correctly when the

report should comply with the ICD-10 scheme. Even since 2015, is it likely that physicians diagnose unintentionally incorrect due to their habits.

5.1.2 RNV3P lacks rigor regarding exposure information and is subject to reporting bias

Florentin et al., (2017) stated that *“several limitations of clinical and “statistical” emergence have been highlighted by Bonnetterre et al. (2008, 2010, 2012) in the context of RNV3P. Caveats of the detection approach through declarative database are manifold: unsystematic and non-exhaustive review of exposure data, dependence of the data on occupational physicians’ expertise (knowledge, methods for exploring exposures, experience, etc.), and reporting bias”*.

5.1.3 Questionable relationship of disease and occupational exposure to MMA

We understand that for reasons of compliance with the General Data Protection Regulation (GDPR) and medical confidentiality, only a small proportion of the detail that may be available in the RNV3P database can be provided on each case in the CLH report. However, the actual level of detail provided in the CLH report does not allow sufficient evaluation of the cases to address all the scientific and regulatory aspects mentioned in chapter 3.

In this regard, the CLH report relies on the high level of so called “attributability” as semi-quantitative indicator for the causal link between occupational exposure to MMA and the development of asthma. Indeed, only cases with a moderate or high level of attributability are presented in the CLH report suggesting not only a pre-selection of the most relevant cases, but also a high incidence of “high attributable” cases with MMA. Further investigation shows that this is indeed not accurate for two reasons.

a) Categorisation

Closer inspection of the coding system used within the RNV3P database reveals a fundamental limitation in the options available to clinicians wishing to specify precisely the chemical agent. This came to light when Healthcare professionals interviewed by ANSES staff reported that they used occupational disease table No. 82 (RG82) “Disorders caused by methyl methacrylate” to encode cases involving exposure to (meth)acrylates other than MMA (ANSES, 2017). As evidenced by the available information on the supposed MMA-cases in the RNV3P database and supported by the published clinical literature, the term “(meth)acrylates” continues to be used extensively by clinicians as a “catch-all” to include a wide range of chemical substances. This broadening of chemical substances within a (meth)acrylate grouping is unhelpful in that it lacks specificity and even includes known respiratory sensitisers, like Cyanoacrylates. As a consequence the CLH wrongly concludes from the disease term “Disorders caused by methyl methacrylate” a direct causal association between MMA and development of asthma in many reported RNV3P cases. The authors of the CLH report despite being aware of this weakness, and having full access to the RNV3P database, failed to interrogate the individual cases to determine if MMA was indeed involved in every case. As a consequence the authors of the CLH report included erroneous data giving a false impression of the prevalence rate.

b) Attributability

The term “attributability” infers that critical aspects of exposure to the suspected agent have been confirmed by the clinician, such as *“patient’s history of occupational exposure, estimated levels and the chronology of the appearance of the disease”* (Bonnetterre et al. 2009). This type of information is a key element in the fundamental information requirements for the assessment of human data as described in ECHA’s endpoint specific guidance (2017; see chapter 3.1.2). While the absence of any

justification for the respective attributability levels assigned to individual cases prevents further analysis and interpretation, the fact that superficial analysis reveals that so many did not involve any exposure to MMA, but were still assigned a high level of attributability, throws serious doubts as to the level of confidence in the RNV3P data.

In summary, prior to a review of the asthma cases attributed to MMA in the RNV3P it is important to have an introductory understanding of the strengths and weaknesses of this database. The RNV3P network has usefulness for exchange of occupational health information however its known diagnosis errors, reporting bias, and the flawed relationship of the diagnosis to MMA exposure severely limit its utility is ability to attribute the cases to MMA exposure specifically.

5.2 Other national occupational health databases cited in the CLH report

The CLH report also cites case reports of asthma attributed to MMA from other National and Regional Health Surveillance Networks in the United Kingdom and Finland in support of their claim that asthma caused by MMA is widespread. These data, as with the data from the RNV3P database necessitate further investigation.

5.2.1 UK's SWORD/THOR/ OPRA/ SHIELD

The CLH report lists 23 actual cases of occupational asthma attributed to methyl methacrylate of UK's THOR/SWORD network, reported between 1989 and 2017, plus one case in UK's THOR/ OPRA network. Only very limited information is available on these cases so that a comprehensive assessment of these cases is not possible.

However, it appears likely that 20 of these in total 24 cases in the UK are identical with the cases which are discussed in the publication of Walters et al. (2017) from a parallel regional surveillance system called "Shield", as Walters is a known and active reporter into the SWORD network (OASYS, 2019).

In January 1989, the UK the UK Midland Thoracic Society's Surveillance Scheme of Occupational Asthma established "Shield". Chest physicians, the Medical Boarding Centre (respiratory disease), and members of the West Midlands Group of the Society of Occupational Medicine implement the scheme. With the introduction of the data protection act in the UK, data availability has been limited to anonymous data about the patient, the agent thought to cause the occupational asthma and audit criteria from the BTS standards of care.

Walters and co-workers published a paper titled "Occupational asthma caused by acrylic compounds from SHIELD surveillance (1989–2014)" in *Occupational Medicine* in April 2017. The authors preface the paper by stating "*Acrylic monomers (acrylates), methacrylates and cyanoacrylates all cause asthma by respiratory sensitisation*". They go on to report that in the West Midlands region within the UK between 1989 and 2014, there were "*20 affected patients out of 1790 total cases of occupational asthma (1%)*". They claim that 20/20 were confirmed by analysis of serial peak flow (PEF) measurements and 3/20 by positive specific inhalation challenge (SIC) tests. Three out of 20 (15%) patients were current smokers and 11/20 (55%) were atopic. Table 2. Lists the 8 cases claimed to be "*caused by predominantly methyl methacrylate (emphasis added)*". Six cases were attributed to MMA and two (5&7) to mixed exposure MMA and cyanoacrylate. Of the 6 MMA cases, one was a prosthetic limb moulder (1); two (2&6) were orthopedic nurses using bone cements; one fabricated tanks and radiators (3); one a dentist (7); one was a midwife (8) and one was an injection moulder that handled polymer not liquid MMA (4).

Only patients 1&6 were confirmed by SIC but no details of how this was done were included in the publication.

The prosthetic limb moulder (patient 1) was described as "laminating carbon- and glass-fibre" He was atopic and had developed rhinitis and asthma symptoms on exposure to cats and grass pollen. In addition to using Orthocryl resin containing methyl methacrylate he made and cut Pedilen rigid-foam body compensations, using a hardener containing methylene diphenyl diisocyanate (MDI) which is a well-recognised cause of occupational asthma. Therefore, MDI rather than MMA may well, if not likely was, the cause of the asthma in this patient.

Of the two orthopedic nurses using bone cements, one was atopic (patient 2) and diagnosed with SIC, the other (patient 6) was non atopic. They both had apparently obstructive airways and the association with MMA was presumably based upon their job description. The positive SIC for the first patient (2) could equally be explained by the irritant properties of MMA vapour as demonstrated by the publication of Pickering since the SIC will have likely formed extremely high concentrations of MMA vapour that would provoke a positive response in a person suffering from asthma. Indeed, the paper states that *“she experienced intermittent asthma symptoms on exposure to airway irritants including chlorine-based cleaning agents”*.

The injection moulder that handled polymer not liquid MMA (patient 4) may have been exposed to MMA vapour during injection moulding but it should be recognised that thermal processing of acrylic and other polymers would have created “cocktail” of other volatile off gases that are normally controlled by local exhaust ventilation so it is not possible to attribute his condition to exposure to a single chemical, MMA.

The tank and radiator fabricator (patient 3) was claimed to have used a MMA-based adhesive and the midwife (patient 7), a tissue adhesive spray – presumably MMA-based. No further details were provided.

So of the 8 claimed cases, two were co-exposure to cyanoacrylates (5&7); one was to polymer (patient 51), one was likely to MDI, or at least it cannot be excluded (patient 1) so in fact there were 4 cases.

Of these 4 cases; one of the orthopedic nurses (patient 2) was atopic. Both were diagnosed on the basis of having asthma and symptoms worsening in the workplace, or in one case (2), under SIC. Both the work related pattern of illness and the positive SIC which could be equally explained as being due to the irritant properties of high concentrations of MMA vapour.

In the case of the remaining 2 cases (patients 3 and 8) no detail are provided upon which to base a judgement of causation and it appears that the conclusion that this was indeed the case, was based upon the a priori conclusion stated at the outset *“Acrylic monomers (acrylates), methacrylates and cyanoacrylates all cause asthma by respiratory sensitisation”* clearly indicating a bias that was carried through to the interpretation of the data.

So in fact the paper of Walters and co-workers included only 4 affected patients out of 1790 total cases of occupational asthma (0.22%) thought to be due to MMA. Of these four, 3 (were presumptive and only based upon the presence of an asthmatic condition and a self-reported claim of working with MMA, without any consideration of other potential confounding factors. Since no details were given as to how the provocation challenge test was done and whether they avoided overtly irritating concentrations it is not possible to determine if this case is indeed indicative of causation of asthma or simply workplace aggravation of an asthma condition by an irritant vapour.

In summary, the 4 cases cited from the UK do not provide strong evidence that MMA causes asthma.

5.2.2 Finnish FIOH and others

The CLH report refers to four potential cases of occupational asthma attributed to methyl methacrylate of Finnish FIOH database, reported between 1997 and 2018. Beside the information that specific inhalation challenges (SIC) with workplace agents were performed, only very limited information is available on these cases so that a comprehensive assessment of these cases is not possible.

For completeness reasons it should be mentioned that the CLH report indicates that “*the Swedish Work Environment Authority (SWEA) received, during the period 2008-2018, a couple of reports of respiratory complaints possibly caused by methyl methacrylate*”. This information is not further discussed in the CLH report. In absence of further details, we accompany this manner.

For Belgium and the Netherlands together, five cases of occupational asthma were briefly mentioned in the CLH report. From the very limited available data we conclude that the cases are potentially linked to exposure to other methacrylates or acrylates and not MMA.

5.2.3 Overall conclusion of the data from other national occupational health databases cited in the CLH report

The other national occupational health databases cited in the CLH report suffer from the comparable limitations to the data within the RNV3P database that limit the usefulness of the data to the point that it cannot be weighted in a formal weight-of-evidence assessment. Where relevant information is provided it does not provide strong evidence that MMA caused asthma in these individuals, rather, all the available evidence is consistent with exposure to an irritant vapour exacerbating a pre-existing or acquired asthma condition.

5.3 Reported publications

The CLH report cited several publications in support of its classification proposal for MMA as causing asthma. The review by the report authors does not take account of available information that places under question the validity of the cited studies. A more valid, detailed review of the reported publications is available in Appendix 9.1 and an overall WoE assessment of all available information is summarized in chapter 6.3.

5.4 Summary of the exposure profile for relevant job sectors

In the CLH report, 79 cases from professional and skill-trade professions were attributed to MMA exposure and constitute the basis of the CLH proposal. 71 of these were taken from the French RNV3P database or other national occupational health databases and 8 from public literature.

Of these 79 cases, 24 were from dental and medical uses and one case from road painting use. The remaining 54 cases were either not attributable to MMA as MMA was not used in this job sector, or co-exposure to other chemicals was highly likely and may have been the cause of the health effect reported. Therefore, 54 out of 79 case were not of high “attributability”.

Of the 24 cases, 20 came from dental technicians that may handle liquid MMA along with numerous chemicals which are described in the Appendix 9.3. In the case of dental technicians, several investigators have linked exposure to other chemicals as being either contributory or the reason for this high level of both contact allergy and respiratory illness (Kusaka et al., 2001; Ergünet al., 2014 and Abakay et al, 2013) in this sector. For this reason, it is not possible to assign high “attributability” to these case studies.

Of the remaining four cases one was an orthopaedic surgeon and three were theatre nurses claimed to use MMA based bone cement. Whilst exposure to MMA is very likely, the information provided on these case studies is insufficient to distinguish between irritant-induced asthma and irritant-provoked effects in pre-existing asthmatics. Hence, they do not constitute evidence of the causation of asthma due to MMA.

Further details are compiled Appendix 9.4.

6 Relevant information on the potential of MMA for occupational asthma missing in the CLH report

Beside the information in the report, there exists further relevant information on the potential of MMA for occupational asthma which is missing in the CLH report for unknown reasons. Other information is significantly underrepresented in the report with respect to its relevance for the assessment. Together with the information provided in the report, the information in this chapter is crucial for a scientifically valid WoE approach.

6.1 Reviews & assessments

The potential of MMA for occupational asthma has been assessed several times in the past, either by authority expert groups or in peer-reviewed journals. The most relevant assessments since 2000 are chronologically compiled in this chapter. These assessments used the majority of publications mentioned in the CLH report plus additional publications (see Appendix 9.2) which partially cover reported database cases (e.g., Walters et al. 2017).

6.1.1 EU Risk Assessment, 2002

The in depth review of the EU-RA (ECB, 2002) covered not only all reported publications - except the later published Obando et al. (2013) and Roth et al. (2017) – but also additional publications as reviewed in Appendix 9.2.

The assessment concluded as follows:

*“A small number of case studies have attempted to link MMA exposure with occupational asthma. Authors reported only immediate responses which are most likely due to an airways irritation. While an immunological mechanism may be deduced in a few cases, the majority of cases do not seem to indicate a mechanism resulting in respiratory sensitisation but due to irritative reactions. It was concluded that there is **no convincing evidence that methyl methacrylate is a respiratory sensitiser in humans**. Thus, the R-phrase R 42 “(for respiratory sensitisation)” is not warranted, however, possible non-specific asthmatic responses due to respiratory tract irritation cannot be excluded and **labelling with R 37 “(for respiratory irritation)” is sufficient for the protection of humans**.”*

Furthermore, *“**there is a need for limiting the risks of MMA concerning skin sensitisation and respiratory tract irritation at several workplaces in the chemical industry, industrial area and skilled trade and during use of casting resins**. For certain inhalation exposure scenarios systemic toxicity gives in addition rise to concern. Risk reduction measures at the community level are recommended.”*

6.1.2 SCOEL, 2005

MMA has been reviewed by SCOEL in 2005 and the following was concluded “*There have been a small number of cases reported of asthmatic reactions associated with occupational exposure to MMA (e.g. Andrews et al 1979; Lozewicz et al, 1985; Pickering et al, 1986; Reynaud-Gaubert et al, 1986; Savonius et al, 1993; Pickering et al, 1993). However, 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 preexisting, generally hyperreactive airways. There are also other features that confound the interpretation of the experiences reported in some of these cases. Overall, there is **no convincing evidence that methyl methacrylate is a significant inducer of asthma in humans** (ESR, 2002; HSE, 1997; Pickering et al, 1993; Pausch et al, 1994).*”

6.1.3 Review of Borak et al., 2011

In their critical review on MMA and respiratory sensitisation, Borak and co-authors came to the conclusion that “*the weight of evidence, both experimental and observational, argues that **MMA is not a respiratory sensitizer***” (2011). It should be mentioned that, in contrast to the CLH report, this review covers all aspects of a scientifically valid WoE approach as proposed by ECA and in the SCHEER memorandum of the EU Commission (see chapter 3.1.3).

In more detail, the review included all types of modelling approaches and *in vitro* or *in vivo* toxicology literature including medical case studies related to the respiratory effects of MMA. Numerous *in silico* and *in chemico* studies indicate that MMA is unlikely to be a respiratory sensitizer. The few *in vitro* studies suggest that MMA has generally weak effects. *In vivo* studies have documented contact skin sensitisation, nonspecific cytotoxicity, and weakly positive responses on local lymph node assay. There were no studies identified in guinea pig and mouse in which inhalation sensitisation has been tested experimentally. Worker health studies reported irritation of eyes, nose, and upper respiratory tract associated with short-term peaks exposures, but there was little evidence for respiratory sensitisation or asthma. Borak identified 19 case reports in the literature that described asthma, laryngitis, or hypersensitivity pneumonitis in workers in various industries exposed to MMA vapour, however, exposures were either not well described or involved mixtures containing other more reactive respiratory sensitising and irritating chemicals.

Borak identified limitations of the available data as follows:

- **Hidden sensitisers as confounding factor in the dental field:** “*Dental materials also contain nonacrylate additives that **are often not listed on MSDS and product labels**. Examples include reaction initiators (e.g., benzoyl peroxide), reaction activators (e.g., tertiary amines such as N,N-dimethyl-p-toluidine 4-tolyl diethanolamine), cross-linking agents (e.g., formaldehyde), reaction inhibitors (e.g., hydroquinone and p-methoxyphenol), and resin carriers (e.g., N-ethyl-4-toluene sulfonamide) (Kanerva et al., 1989, 1997; Van Der Walle et al., 1982a). All of these additives are known contact sensitizers and **several are known or suspected respiratory sensitizers and/or respiratory irritants** (Enoch et al., 2009; Geurtsen, 2000; Kanerva et al., 1997; Van Der Walle et al., 1982a)... In some studies, **researchers failed to list all known sensitizing components** in the materials of concern. For example, responding to inquiries by an ECETOC task force about the cases reported in dental workers (Savonius et al., 1993), the authors acknowledged that “workers had been exposed to other*

acrylates than methyl methacrylate,” that the material used in SIC testing was “impure,” and that subsequent analysis determined that dental materials “contain many additional acrylates that have not been declared [sic] in the MSDS... additives and additional impurities” (Kanerva, 1993)”

- **Difficulties to distinguish allergenic from non allergenic/ irritative effects** of epidemiological studies: “The epidemiological studies ... did not verify self-reported diagnoses and, as described below, none could determine whether noted effects were specifically due to sensitization or irritation. Moreover, as discussed earlier, it can be clinically difficult to determine that an individual suffers sensitizer- versus irritant-induced respiratory disease.”
- **Weaknesses of the WoE approach:** “None of the studies described below included reviews of medical records or external evidence of MMA-related disease. Another source of uncertainty is the limited adequacy of work site exposure assessments. Most industrial workers are exposed to mixtures, but reported exposure assessments generally considered only MMA.”
- **Methodological limitations during diagnosis:** “A third source of uncertainty derives from the diagnostic tests commonly used in work site screening for respiratory diseases such as asthma. Tests such as spirometry and peak expiratory flow rates (PEFRs) have only limited predictive value for asthma, especially when performed in nonstandard ways (Bernstein et al., 2006a; Burge et al., 2006; Nicholson et al., 2005; Tarlo et al., 2008)”
- **Cross-reactivity as confounding factor:** “A further complication is **that many of the agents cross-react, raising** uncertainty about which agent was responsible for induction of hypersensitivity. Such cross-reactivity has been demonstrated in animals and humans using skin test protocols. In guinea pigs, cross-sensitization has been shown between MMA and the following acrylates and methacrylates: ... In addition, concomitant sensitization to reaction inhibitors (hydroquinone and p-methoxyphenol) occurred with 7 of 11 methacrylates reported to be otherwise >99% pure; levels of those inhibitors in the methacrylate mixtures were not reported (Van Der Walle et al., 1982a).”

Finally, it should be mentioned that this review addresses all publications in Appendix 9 with exception of the younger publications of Obando et al. (2013) and Roth et al. (2017).

6.2 Relevant publications not cited in the CLH report

Several primary literature has been identified by industry and various organisations including OECD (2002) and the ECB (2002) when reviewing MMA and asthma but that were not included in the sources of the CLH report for unknown reasons. As with the publications cited in the CLH report they too deserve detailed analysis in order to determine their reliability and strength.

A detailed review is available in Appendix 9.2.

6.3 Summary on the available information

6.3.1 Reviews & assessments

All listed reviews and assessments in this chapter came to the unanimous conclusion that there is no relevant evidence that MMA is a causative agent for occupational asthma. Thus, authorities relinquish from classification in the past. With respect to the new information in the CLH report and its identified limitations discussed in chapters 3 and 5.1 plus Appendix 9.1, there are no reliable new information presented in the report which have the potential to change the current position.

6.3.2 Publications

The EU-RA (ECB 2002) concluded on the identified case studies available at that time (2000): *“Summarizing 6 case reports (Lozewicz et al., 1985; Pickering et al. 1986; Reynaud-Gaubert et al., 1991; Savonius et al., 1993a,b) have implicated MMA as a respiratory sensitizer. Both the Lozewicz and Reynaud-Gaubert publications reported only immediate responses which may have been simply due to irritant provocation of the airways by MMA. Information critical to the interpretation of the 3 cases reported by Savonius (1993a,b) is not available and it is not possible to conclude that the symptoms observed resulted from exposure to MMA. Pickering et al. (1986) reported a delayed asthmatic response in 1 individual which would not normally be associated solely with an irritant provocation. The Task Force believes, however, that because of the uncertainties associated with the challenge to MMA, this study cannot be taken as a definitive case report of respiratory sensitization. In addition, these case reports must be placed in context opposite the lack of evidence of a respiratory sensitization effect of MMA in studies of large groups of workers occupationally exposed to MMA.”*

Since 2000, there have been other case studies reported (Obando, Roth and Scherpeel) however, these do not contain any further reliable information on the causal link between MMA and development of asthma and therefore do not change the conclusion arrived at by the ECB in 2002.

Moreover, no new cross sectional studies have been conducted since 2002 when the EU-RA was completed so the still currently available information from worker health studies does

support the conclusion that MMA is an irritant vapour but does not support the conclusion that MMA causes asthma even in workers with peak and lower long-term exposure to, what were historically, relatively high levels of MMA.

In summary, there have been a number of case studies reported in the clinical literature of individuals reporting the development, or provocation, of asthma symptoms at work. MMA and methacrylates have been cited in a number of these cases as being involved. In some cases this assertion is false and based upon inaccurate or misleading information, or presumed based upon the type of employment. Often the substances actually being used were other chemistries including cyanoacrylate, styrene, solvents, acrylic esters (other than MMA) and acrylic powder/dust including Polymethylmethacrylate (PMMA). For those case studies where MMA has been used within provocation challenge tests (SIC) the SIC test used conditions aimed to simulate the normal work activity in a confined space, and this will lead to very high concentrations of MMA vapour, well in excess of several hundred ppm. Such high levels of vapour are irritating to the respiratory system in normal persons, never mind in individuals that have been referred because they are suffering from asthma. It is not surprising, therefore, that SIC using liquid MMA in this way provoke asthmatic responses and are considered positive.

The moot point is whether MMA caused the development of the asthma or whether exposure to MMA aggravated either a state of pre-existing disease, or a disease that had developed concurrently due to another agent or agents. It should be recognised that it is extremely difficult to prove “causation” in such circumstances retrospectively since often the only witness to this is the patient and memories are not without error. Furthermore, when such individuals are in the process of claiming occupational illness it is not unrealistic to presume that such recollections might be open to misinterpretation or bias.

The fact remains that a number of individuals in certain industries such as dental technicians and workers handling cold cure cements that do develop bronchial reactivity and asthma. The question is what causes it? MMA is often implicated as it is “recognised” in clinical spheres to be “a cause of asthma”, so why look further. The confusion regarding chemistries that may contain the term “acry” or may be other plastics seems to confuse the diagnostic process even further. It is, however, contradictory that two comprehensive cross-sectional worker-health studies in the cast acrylic sheet industry that predominantly uses liquid MMA to make PMMA polymer, and that has had high level exposure over many years, does not reveal a problem with MMA causing asthma. In the case of dental technicians, several investigators have linked exposure to other chemicals as being either contributory or the reason for this high level of both contact allergy and respiratory illness (Kusaka et al., 2001; Ergünet al., 2014 and Abakay et al, 2013).

7 Conclusions

The harmonised classification and labelling (CLH) process is a useful mechanism to ensure an adequate risk management of a chemical within the EU. A respective proposal “*consists of the CLH report and any other supporting information, which is intended to be a ‘stand-alone’ document and must contain sufficient information to allow an independent assessment of physical, health and environmental hazards based on the information presented*” (ECHA, 2019).

An CLH proposal “*must contain sufficient information to allow an independent assessment*” according to ECHA. However, the WoE approach within this CLH reports lacks fundamental scientific standards as defined by ECHA and the European Scientific Committee SCHEER. Seen on its own, the disregard of these standards results in a misinterpretation of the weak evidence that the approach does present and does not take into account conflicting evidence of higher reliability from other publicly available sources.

For example, the review of publicly available literature detected fundamental deficiencies in the coding schemes of the RNV3P database which is used as a main primary source of information in the CLH. The code for MMA is used for the whole (meth)acrylates family, thus seriously questioning the claimed “*high attributability*” of asthma diagnosis and MMA exposure for all RNV3P cases.

For another example, 54 of in total 79 cases in the CLH report were either not attributable to MMA as MMA was not used in the respective job sectors, or co-exposure to other chemicals was highly likely and may have been the cause of the health effect reported. The likelihood of the exposure of a patient to MMA as causative agent for the respective diagnosis (the so called “*attributability*”) has been insufficiently checked for plausibility. As a consequence, 54 out of 79 case were not of high “*attributability*”.

Thus, the WoE approach of the CLH proposal is not balanced and not scientifically justified.

The lack of fundamental understanding is also true for endpoint specific aspects. The CLH report proposes that Methyl Methacrylate (MMA) should be classified as Respiratory Sensitiser, Cat. 1 H334 according to CLP Regulation and based on human data. For respiratory sensitisation, evidence for a biphasic mode of action with an initial induction phase followed by an elicitation phase has to be provided so that the human data allow for the determination of “*causation*” of the development of asthma and not simply that it “*provokes*” or “*aggravates*” a pre-existing condition.

This CLH proposal however does not make efforts to clearly distinguish between respiratory irritation effects (for which MMA is already classified) against the respiratory sensitisation effects claimed in the CLH proposal, neither in general nor on a case-by-case basis. Therefore, a fundamental piece of information for a valid WoE approach for the respiratory sensitisation potential of MMA is missing.

In the limited time available, we have made an alternative assessment that on one hand refers to a broader database than the CLH report and that on the other hand complies to the above mentioned standards of ECHA and SCHEER. Irrespective of the potential mode of action, our initial considerations on the prevalence of potential asthma cases in potential relation to MMA exposure indicate that the prevalence is low in the exposed cohorts. At the same time, also in the exposed cohorts, it is orders of magnitude below the general prevalence of asthma (see chapter 3.1.1.2 and Appendix 9.3.8).

In summary, the respective WoE approach more than adequately demonstrates a lack of confidence in the CLH proposal that MMA is a causative agent for occupational asthma. Instead, all available evidence reviewed in the literature of sufficient strength confirm that MMA has the potential to provoke respiratory irritation in pre-existing asthma cases. As such, there is sufficient doubt in the strength of evidence supporting classification of MMA as respiratory sensitiser.

Also, following the assessment strategy of ECHA’s endpoint specific guidance (2017), MMA has not to be considered as respiratory sensitiser in absence of structural alerts and based on the aforementioned scientifically valid WoE approach.

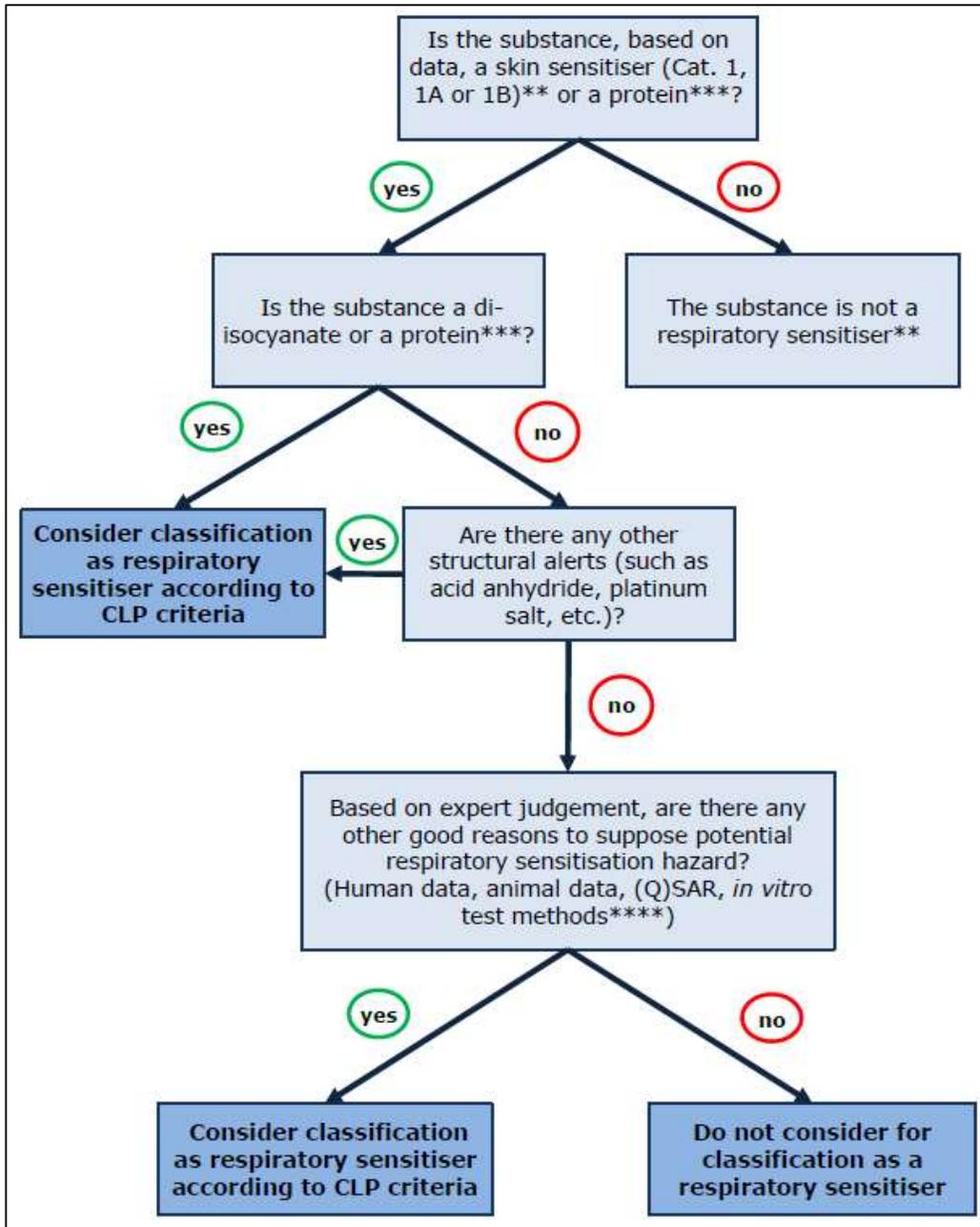


Figure 1: Assessment strategy for respiratory sensitisation data (taken from ECHA 2017)

As a final consequence, we see a classification of MMA as respiratory sensitiser as not justified and thus we propose that the current Annex VI entry remains unchanged.

8 References

- Amoore JE, Hautala E (1983). Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution; *J. Appl. Toxicol.* 3: 272-290
- Abakay A et al. (2013). Frequency of respiratory function disorders among dental laboratory technicians working under conditions of high dust concentration. *European review for medical and pharmacological sciences.* 17. 809-14
- Arts J and Kimber I (2018). Letter to the Editor: Azodicarbonamide (ADCA): a reconsideration of classification as a respiratory sensitiser. *Regul Toxicol Pharmacol* 94, 332-333
- Alberts WM and Brooks SM (1996). Reactive airways dysfunction syndrome. *Curr Opin Pulm Med* 2, 104-110
- Brooks SM et al. (1985). Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest* 88, 376-384
- ANSES (2017). Assessment of risks for professionals exposed to products used in nail care and decoration activities. ANSES Opinion/ Collective Expertise Report on Request No. "2014-SA-0148", Oct 2017
- Boneterre V et al. (2009). Programmed health surveillance and detection of emerging diseases in occupational health: contribution of the French national occupational disease surveillance and prevention network (RNV3P). *Occup Environ Med* 2010; 67: 178-186
- Cromer, J and Kronoveter, K (1976). A study of methyl methacrylate exposures and employee health in five cast sheet plants. Prepublication copy. NIOSH, Cincinnati OH
- ECETOC (1995). Joint Assessment of Commodity Chemicals No. 30, Methyl Methacrylate. ISSN-0773-6339-30. ECETOC, Brussels
- ECHA (2010). Practical guide 2: How to report weight of evidence. ISBN-13: 978-92-9217-028-8
- ECHA (2011). Guidance on information requirements and chemical safety assessment Chapter R.4: Evaluation of available information version 1.1, ECHA-2011-G-13-EN
- ECHA (2017). Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance ISBN: 978-92-9495-970-6
- Engasser P, et al. (2000). Cosmetologists. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, editors. *Handbook of occupational dermatology*. Berlin: Springer Verlag, p 893–898

Ergün, D et al. (2014). Pneumoconiosis and respiratory problems in dental laboratory technicians: Analysis of 893 dental technicians. *International journal of occupational medicine and environmental health*. 27. 10.2478/s13382-014-0301-9

EU SCHEER, Scientific Committee on Health, Environmental and Emerging Risks (2018). Memorandum on weight-of-evidence and uncertainties, Revision 2018; https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_014.pdf

EU (2008). Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008

European Chemicals Bureau (2002). European Union - Risk Assessment Report on Methyl methacrylate. European Union - Risk Assessment Report, Vol. 22

Evans GS et al. (2008). Chemical pollution, respiratory allergy and asthma: a perspective. *J Appl Toxicol* 28, 1-5

Florentin, A. et al. (2017). Contribution of job-exposure matrices for exposure assessment in occupational safety and health monitoring systems: application from the French national occupational disease surveillance and prevention network. *Int Arch Occup Environ Health* (2017) 90:491–500

HSE, UK Health and Safety Executive (1995). Methyl methacrylate. Criteria document for an occupational exposure limit. ISBN 0 7176 0945 6

Jedrychowski WA (1982). Styrene and methyl methacrylate in the industrial environment as a risk factor of chronic obstructive lung disease. *Int. Arch. Occup. Environ. Health* 51, 151-157.

Jedrychowski WA, et al. (1982). The evaluation of the effects of occupational exposure to styrene and methyl methacrylate on respiratory system. *Przegl. Lek* 39, 299-303. [Polish; *Excerpta Medica Toxicol* 1, 643]

Jedrychowski WA and Fonte R (1984). Chronic chest symptoms and airflow obstruction among workers in the chemical industry. *G Ital Med Lav*6: 225 - 233

Kimber I, Pemberton MA (2014). Assessment of the skin sensitising potency of the lower alkyl methacrylate esters. *Regul Toxicol Pharmacol* 70; 24–36

Kimber I, et al. (2011) Chemical allergy: translating biology into hazard identification and characterization. *Toxicol Sci* 210 (S1), S238-S268

Kimber I, et al. (2001). Chemical respiratory allergy: classification and labelling. *Toxicology* 167, 159-162

Klimisch HJ et al. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data; *Regul Tox and Pharmacol* 25 1-5

Klonne DR et al. (1987). Dimethylethanolamine: Acute, 2-week, and 13-week inhalation toxicity studies in rats. *Fundam Appl Toxicol*. 9:512–521

- Kusaka, Y et al. (2001). Metal-Induced Lung Disease: Lessons from Japan's Experience. *Journal of Occupational Health*. 43. 1-23. 10.1539/joh.43.1
- Lau A and Tarlo SM (2019) Update on the management of occupational asthma and work-exacerbated asthma. *Allergy Asthma Immunol Res* 11, 188-200
- Leung HW and Blaszcak DL (1998). The skin sensitization potential of four alkylalkanolamines. *Vet Hum Toxicol*. 40:65–67
- Marez T et al. (1993). Bronchial symptoms and respiratory function in workers exposed to methylmethacrylate. *Br J Ind Med*. 50:894–897
- Marez T et al. (1991). Increased frequency of sister chromatid exchange in workers exposed to high doses of methylmethacrylate. *Mutagenesis* 6: 127-9.
- Mauger EA et al., for the Asthma Clinical Trials Network (2001). Summarizing methacholine challenges in clinical research. *Control Clin Trials* 22, 244S-251S
- Elf Atochem (1996). Correspondences regarding study of Marez et al., 1993
- Mizunuma K et al. (1993). Biological monitoring and possible health effects in workers occupationally exposed to methyl methacrylate. *Int Arch Occup Environ Health* 65, 227-232
- Muttray, A et al. (1997). Effects of methyl methacrylate on the sense of smell. *Central Europ. J. Occup. Environ. Med*. 3, 58-66
- Nendza, M. et al. (2010). Data quality assessment for in silico methods: a survey of approaches and needs. Chapter 4 in: Cronin, M.T.D., Madden, J.C. (eds.) *In silico toxicology, principles and applications*. RSC Publishing, Cambridge, UK. ISBN 978-1-84973-004-4
- New Jersey Department of Health (2010). Hazardous Substance Fact Sheet: Dimethylaminoethanol; <http://nj.gov/health/eoh/rtkweb/documents/fs/3111.pdf>
- OASYS (2019). A descriptive study of occupational asthma due to acrylic compounds - study protocol. REC reference 16/YH/0308. http://www.occupationalasthma.com/occupational_asthma_pageview.aspx?id=6250
- Obando S. et al. (2013). Occupational asthma due to polyvinyl chloride and methylmethacrylate, “hidden in an adhesive”. *Clinical and Translational Allergy* 2013 3(Suppl 1):P32
- Onisep (Office national d'information sur les enseignements et les professions) (2018): Job description “Assistant/e dentaire”; [www.onisep.fr/content/download/462388/9999764/file/assistant\(e\)_dentaire.pdf](http://www.onisep.fr/content/download/462388/9999764/file/assistant(e)_dentaire.pdf)
- Paris, C. et al. (2012). Work-related asthma in France: recent trends for the period 2001-2009. *Occup Environ Med* 2012; 69:391-397
- Pausch, Hoffer, Clajus, Lehr and Jacobi (1994): Medical examination of workers in acrylic sheet production exposed to methyl methacrylate. *Pub. Rohm Gmbh Chemische Fabrik*

- Pickering, CAC et al. (1993): A study of the prevalence of occupational asthma at the ICI acrylics site at Darwen, Lancashire. The North West Lung Centre, Manchester, UK
- Reynaud-Gaubert M, et al. (1991). Astme professionnel au méthyl-méthacrylate. Presse Med. 20, 386
- Röhm GmbH (1994): Confidential report: Lungenfunktionsanalysen und Geruchssinnprüfungen in einem Acrylglasproduktionsbetrieb. Schmitt, B., Röhm GmbH, Darmstadt
- Roth, E. et al (2017). Arbejdsbetinget astma hos en ortopædkirurg. (Occupational asthma in an orthopaedic surgeon) / In: Ugeskrift for Læger, Vol. 179, No. 19, V01170028, 2017, p. 1682-1684
- Savonius B et al. (1993). Erratum: occupational respiratory allergy caused by acrylates. Clin Exp Allergy 23, 712
- SGS (Société Générale de Surveillance). Insight into Cosmetics Recalls Since EU Cosmetic Regulation Implementation; SGS: Geneva, Switzerland, 2014
- Smyth HF, et al. (1951). Range-finding toxicity data: List IV. AMA Arch Ind Hyg Occup Med. 4:119–122
- UNPPD, Union Nationale Patronale des Prothésistes Dentaires (2013): <https://www.unppd.org/>
- Uriarte SA et al. (2013). Occupational asthma due to polyvinyl chloride and methyl methacrylate in a plumber. Investig Allergol Clin Immunol. 23(6):437-8
- Vallieres M et al. (1977). Dimethyl ethanolamine-induced asthma. Am Rev Respir Dis. 115:867–871
- Walters GI et al. (2017). Occupational asthma caused by acrylic compounds from SHIELD surveillance (1989–2014). Occupational Medicine 2017; 67: 282–289
- Wittczak T et al. (1996). Bronchial asthma with inflammation of the nose mucous membrane induced by occupational exposure to methyl methacrylate in a dental technician. Med Pr. 47(3):259-66
- WHO (2019): Bronchial asthma, Fact sheet N°206; <https://www.who.int/mediacentre/factsheets/fs206/en/>
- Zock JP et al. (2001) Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. Scand J Work Environ Health 27, 76-8

9 Appendix

9.1 Publications cited in the CLH report

9.1.1 Marez et al. 1993

This paper reports a cross-sectional study conducted in France that sought to investigate adverse respiratory effects in workers exposed occupationally to methyl methacrylate (MMA).

The authors concluded that: 'exposure to MMA seems to be responsible for a mild airways obstruction, but that further study on a larger population would be useful'.

The study compared 40 exposed workers, with 45 controls. Respiratory measurements were performed before, and at the end of, an 8 hour shift. No differences between exposed and control groups in any spirometric values were recorded before the shift. At the end of the shift there was a small, but statistically significant, reduction among the control group in maximum respiratory flow (MEF) at 50% of forced vital capacity (MEF₅₀). All other measurements of lung function did not differ between the groups. The only other finding was that chronic cough was apparently more common among the exposed workers.

The study suffered from a number of serious limitations, among the most important being: (a) the relatively small numbers of subjects evaluated, (b) possible previous exposure among the test group to other respiratory irritants, (c) lack of any information on temporal associations between exposure to MMA and lung function, and (d) the use of a passive sampling technique for measuring exposure levels of MMA that the author of the paper had previously acknowledged to be inaccurate (HSE, 1995).

It might be that among this workforce exposure to MMA resulted in some mild respiratory irritation, but the changes observed were modest, and most lung function parameters did not differ between the exposed and control groups. The conclusion reached by the UK Health and Safety Executive was that the slight increase in airways resistance (MEF₅₀) observed during an 8 hour shift was indicative of temporary upper respiratory tract irritation (HSE, 1995). It is probably also the case that the levels of exposure to MMA reported in the paper were incorrect and underestimated true levels.

It is also worth noting that then serving occupational physician at the plant where the study was conducted had found no adverse respiratory effects in workers exposed to MMA.

In conclusion, there is no evidence that exposure to MMA was associated with the development of allergic sensitisation of the respiratory tract, or with occupational asthma. At most, the study suggested that some workers experienced mild respiratory tract irritation in response to MMA.

It is concluded also that this study is of low reliability, and unsuitable for use in a WoE assessment.

This assessment is in close accordance with that of the OECD SIDS/ EU RA (2002) which reads as follows: *"In this study, only a small population was investigated (including 13 workers without smoking history). There are no data whether the exposed people had ever had long-time exposure to other respiratory irritants. Monitoring time to estimate the methyl methacrylate concentration using*

a passive sampling technique on activated charcoal was eight hours. Two single respiratory measurements were done, one before and the second during the work shift. Data collection was not repeated, no data are available on the correlation of the findings to the mean or peak concentrations. There are some doubts therefore on the accuracy of the exposure values that have been presented. In addition this technique would not detect short term high level exposure."

9.1.2 Röhm GmbH 1994

This is an internal company report of studies conducted of workers engaged in the production of acrylic sheet and who were exposed to MMA. The objective was to determine whether exposure to MMA in the workplace was associated with adverse respiratory effects. This study is available as manuscript and was reviewed and used for the EU-RA (ECB, 2002) as Pausch et al. 1994. Furthermore, confidential exposure data pertaining to these workers and this facility was provided to the EU CA for risk assessment for MMA.

The conclusion drawn was that exposure to MMA was associated with some acute reversible signs of upper respiratory tract irritation, but there was no evidence for allergic sensitisation of the respiratory tract or occupational asthma.

The study was based on a self-administered questionnaire and anterior rhinoscopy using a speculum. The study population comprised a total of 211 male workers with an average of 8.8 years working in an acrylic sheet production plant. Exposure levels were determined using personal air sampling monitoring over an 8 hour period.

No self-reported subjective symptoms of any significance were recorded. Short term exposure to MMA at levels of 100ppm or more resulted in acute irritation of the nose and upper respiratory tract (and eyes) that resolved quickly after cessation of exposure.

The study has a number of limitations, including the use of a self-administered questionnaire and the absence of a control group. Nevertheless, the data do indicate that under conditions of exposure to MMA that resulted in reversible respiratory tract irritation there was no evidence for allergic sensitisation of the respiratory tract.

In conclusion, this study found no evidence that MMA caused allergic sensitisation of the respiratory tract or induced occupational asthma. The significant limitations of this study render it inappropriate for use in a WoE assessment.

9.1.3 Pickering et al. 1986

This paper describes a single case study of an orthopaedic theatre nurse who on a regular basis handled and prepared bone cement (associated with exposure to MMA) and developed respiratory symptoms.

The authors suggested that exposure to high peak concentrations of MMA during the preparation of bone cement induced occupational asthma characterised by wheezing and breathlessness within minutes of mixing cement.

Open bronchial provocation tests were reported to stimulate a late (6 hour) asthmatic reaction.

This case report does not provide compelling evidence that MMA exposure resulted in occupational asthma. There are a number of considerations in this respect, including the fact that initially at least there was no clear association between symptoms and the workplace environment.

Moreover, the bronchial provocation testing as described in the paper has limitations because: (a) irritant levels of the provocation material were used (and lower levels failed to elicit a response), (b) there were no challenges performed with a control material, and (c) an open challenge was conducted – because it was not thought possible to ‘blind’ the subject to the test material (due to the colour and odour of MMA).

Due to these factors it cannot be concluded in this case that exposure to MMA had driven sensitisation of the respiratory tract, or the development of asthma. It is possible that asthma acquired from some other cause might have resulted in the subject displaying increased reactivity to irritant exposure levels of MMA in the workplace.

In conclusion, there is no evidence that the subject of this case study had developed sensitisation of the respiratory tract to MMA. The likelihood is that symptoms were associated with brief high (irritant) levels of exposure to MMA.

9.1.4 Savonius et al. 1993a & b

This paper reports a survey of 3152 subjects that were examined for suspected occupational respiratory disease at the Institute of Occupational Health in Helsinki. Of these subjects some 880 were diagnosed as having “*occupational asthma/respiratory disease*”. It was reported that 18 cases were caused by acrylates (12 by cyanoacrylates, 4 by methacrylates and 2 by other acrylates). However, in an erratum published subsequently (Savonius et al. 1993b), the authors confirmed that MMA was apparently implicated in 3 cases.

The authors suggested that: “*cyanoacrylates and methacrylates may cause respiratory hypersensitivity*”.

Of these 3 cases thought to be associated with MMA (designated M1, M2 and M3 in the paper) it is possible to discount 2 with respect to possible MMA-induced respiratory effects. Patient M1 was found not to have an MMA-specific response, and patient M2 had not been exposed to MMA.

The single case that therefore warrants attention is M3, a female dental technician. This patient experienced tickling in her throat, cough and chest tightness at work, with the symptoms subsiding during sick leave and vacations.

Although challenge of this subject with MMA resulted in a transient drop in peak expiratory flow (PEF) compared with a placebo control, no non-specific/irritant challenges were performed. Importantly also, a skin prick test (SPT) performed with methyl methacrylate was negative.

There are no data to suggest that this subject had developed respiratory sensitisation to MMA. In fact, the negative SPT suggests that sensitisation had not been acquired. It is probable, therefore, that hyperreactivity associated with an increased susceptibility to non-

specific respiratory irritation resulted from some other cause. Certainly it is likely that exposure to substances other than MMA would have occurred in the workplace.

In conclusion, this study is of moderate reliability, and although suitable for use in a WoE assessment it is of low strength given the absence of evidence linking MMA with the development of sensitisation of the respiratory tract, or acquisition of occupational asthma.

The EU RA (2002) concluded on this study analogously that “*consideration of the available data from the 3 cases reported by Savonius et al. (1993a,b) shows no convincing evidence of respiratory sensitisation by MMA.*”

9.1.5 Uriarte et al. 2013

The case described in this publication is identical to that in

Uriarte-Obando, S, Fernández-Nieto M and Sastre, J (2013). Occupational asthma due to polyvinyl chloride and methylmethacrylate, “hidden in an adhesive”. *Clinical and Translational Allergy* 3(Suppl 1):P32

The authors describe “*occupational asthma caused by PVC and methylmethacrylate as shown by specific bronchial challenge to these agents*”. The authors state that they diagnosed occupational asthma in a 48-year-old plumber who was exposed to polyvinyl chloride and MMA. The patient reportedly had no history of atopy. The patient developed progressive dyspnea and dry cough over a 3-year period that was triggered at work and persisted outside of work. The authors suggest his symptoms were the result of exposure to an adhesive called Tangit, whose components were described in the paper as being PVC powder and MMA. The authors claimed that the Tangit adhesive provoked late asthmatic response with a maximal fall in FEV1 of 33% at 7 hours. They also claimed that PVC powder and MMA generated dual asthmatic responses, with a maximum drop of 17% at 30 minutes and 17.3% at 7 hours, 22% at 2 minutes and 20% at 9 hours, respectively. The authors also presented that worker did not present skin lesions or used protective exposure means (assumed to mean skin or respiratory).

The premise of this paper is that MMA is found at trace levels in the Tangit product. However, this was not confirmed when the manufacturer (Henkel) of the product, Tangit, was contacted. Thus, MMA cannot be associated with this occupational case study. There is also inadequate information relating to the occupational exposure. The manufacturers state that Tangit is a solvent, not a PVC powder as described by the authors. Thus, the use of and manipulation of the glue would likely lead to significant inhalation exposures. The safety data sheets say the product should be used in well ventilated rooms so again there is no indication of the occupational exposures which were conducted in a 7m³ room. It is also important to consider other known irritants would cause the patient to have a significant drop in their FEV1 after a specific inhalation challenge.

The Uriarte et al. (2013) and Uriarte-Obando et al. (2013) publications have major scientific deficiencies and, therefore, are unsuitable to relate the development of asthma in this worker to exposure to MMA, or even PVC. The fact that the product in question does not contain MMA makes it impossible to draw conclusions on what generated the individual’s asthma.

9.1.6 Roth et al. 2017

The paper reports a clinical case of an orthopaedic surgeon who displayed cough and dyspnoea that was associated with his work based on improvement of symptoms when he was on holiday. Spirometry showed normal FEV1 and FVC with slightly increased airways resistance (82% of expected). The individual was not atopic and had reported normal IgE levels and no display of eosinophilia. However, he did give a positive response to methacholine indicating bronchial hypersensitivity.

The authors performed no challenge test with MMA, so they are making an assumption that MMA is the cause of the observed work-related asthma symptoms. The causal link between MMA and asthma was concluded on the basis of MMA being an irritant vapor and the assumption based upon the patient's description of his medical history that bronchial hypersensitivity had developed during the course of his work and exposure to bone cements. No attempt was made to determine the composition of the bone cement nor was there any attempt to distinguish between workplace exacerbation of a pre-existing disease or a disease that was coincidentally caused by some other agent(s). It is known that when mixing bone cement Pickering (1986) high levels of exposure to MMA can occur in the first few minutes. Consequently, confounding effects of direct irritation on the respiratory tract were possible.

Overall it is concluded that the Roth et al (2017) study provides suitable evidence to be use in a WoE approach but it lacks any strong evidence linking MMA as the causative agent. Moreover, and most important, there is no consideration for other ingredients/chemicals that could be causative agent.

9.1.7 Scherpeel et al. 2004

The author's main conclusion of the paper is that the observations presented in the paper demonstrate the risk of the development of not only pneumoconiosis or asthma, but also hypersensitivity pneumonitis to MMA. Specifically, the paper reports two cases of hypersensitivity pneumonitis and the authors claim the cause of it is due to inhalation of MMA which occurs within the first weeks of exposure. The dental technicians' exposures were from polishing and grinding prosthesis which generate exposure to dusts and chemicals. For both individuals, however, there is no information on their health history which makes it difficult to know if they were pre-existing asthmatics with bronchial hypersensitivity that were reacting to potential irritant chemicals in the workplace.

It is clear from the description of the symptoms and there timing that these two technicians who demonstrated major dyspnoea with cough for weeks was due to an occupational exposure. What is not clear is what role, if any, MMA played in these symptoms. There is no description of how they were exposed to MMA from polishing and grinding of PPMA. In Case 2, the technician was exposed to aerosolized particles of MMA with presentation of moderate dyspnoea. There was no follow-up exposure with the other technician, Case 1. Although MMA showed abnormalities in the provocation study there is no clear evidence that it was the causative agent. If MMA is solely responsible then a provocation test with other minerals used in the laboratory would have been negative in a provocation study. However, they were not tested. It is known that there can be exposures to MMA when products are being mixed in the workplace (Pickering 1986) and, consequently, they could be a confounding factor due to their irritant effects. It is widely known that dental technicians are exposed to a wide range of mineralogical (aluminum, antimony, arsenic, barium, beryllium, cadmium, chromium, cobalt, copper, iron, lithium, manganese, mercury, nickel,

platinum, rhodium, rare earth metals, titanium, uranium, vanadium, welding, zinc, zirconium) dusts (Kusaka, 2001), sand (Ergünet al., 2014) and other dusts (Abakay et al, 2013) and chemicals that could equally be responsible for the high prevalence of respiratory ill-health in this sector.

Overall it is concluded that the Scherpeel et al (2004) study is of moderate reliability with one case study being more helpful than the other. However, it is weak in demonstrating any quantitative evidence linking MMA with the development (causation) of asthma.

9.1.8 Leggat and Kedjarune 2003

The Leggat and Kedjarune paper reviews the toxicity of MMA and does not contain any original data. They specifically mention MMA's association with causing hypersensitivity, asthmatic reactions, local neurological symptoms, irritant and local dermatological reactions. The paper is not well written, and the main message of the paper is that MMA exposures should be reduced, especially for dental staff who they say should avoid direct contact with MMA and the rooms where it is used should be ventilated well. The only reference to MMA and asthma is in the citation of the paper by Wittczak et al. (1996) The conclusion of this paper is that MMA "*may*" cause asthma (probably atopic) in some persons occupationally exposed.

The authors state that despite MMA's widespread use, the toxicity of the MMA is not widely known. The paper, however, provides no new insights into understanding the toxicity MMA in dental practices. One major deficiency of the paper is that the understanding of exposure to MMA or other constituents is not well covered for any of the toxicities mentioned in the paper.

This paper is of low value with no new information and is unsuitable for use in a WoE assessment of MMA's association with causing asthma.

9.2 Relevant publications not cited in the CLH report (to be considered under a valid WoE approach)

9.2.1 Jedrychowski, W. 1982

The OECD SIDS/EU RA included the paper by Jedrychowski 1982 along with his other paper on the same study in the same year (Jedrychowski et al., 1982) and the follow-up study published by the same author, two years later (Jedrychowski and Fonte, 1984.) These were summarized in both the OECD SIDS and EU RA using the same language as follows:

“Jedrychowski (1982) and Jedrychowski et al. (1982) studied respiratory symptoms in an industrial population consisting of 454 males exposed to MMA (up to 95 ppm) and styrene, and 683 control males who were not exposed to either material. The workers were evaluated by standardized interviews on chest symptoms and by lung function testing (measurement of FEV₁). The authors reported no difference in the prevalence of chronic chest symptoms between the 2 groups of workers, but did observe that the frequency of lung obstruction was twice as high in the group of workers exposed to MMA and styrene compared to the control group. Surprisingly, a large proportion of the cases of lung obstruction did not show any chronic chest symptoms, however, because of the mixed exposure, it is considered that the effects cannot be attributed to any single chemical. A standardized questionnaire and spirometry study were conducted on a group of 4717 male chemical industry workers in Poland. The prevalence of chronic bronchitis, bronchial asthma and obstructive syndrome was evaluated in relation to the variety of chemicals used on the chemical plants. As expected, increased levels of chronic bronchitis, asthma and obstructive syndrome were found in groups of subjects of advanced age and amongst smokers. The frequency on asthma and obstructive syndrome was higher in the chemical industry workers than in the general Polish population, but the frequency of chronic bronchitis was comparable in the 2 groups. The authors concluded that exposure of 1 group of the workers to styrene, benzene and MMA was responsible for the increased prevalence of the pulmonary symptoms observed (Jedrychowski and Fonte, 1984). Due to the mixed nature of the exposures to these agents, it is not possible to attribute the effects observed to any single chemical.”

Comments on the reliability of the Jedrychowski studies

The follow up study and paper by Jedrychowski and Fonte (1984) Jedrychowski concluded that mixed exposure to styrene, benzene and MMA was responsible for the increased prevalence of the pulmonary symptoms observed in the original study by Jedrychowski (1982). Due to the mixed nature of the exposures to these agents, it is not possible to attribute the effects observed to any single chemical, such as MMA.

Conclusion on the reliability of the Jedrychowski studies

Overall it is concluded that the studies of Jedrychowski are of low reliability and unsuitable for use in a WoE assessment.

9.2.2 Mizunuma, K. 1993

Both the OECD SIDS and EU-RA use the same language to describe the paper by Mizunuma as follows:

“Six of 32 male workers exposed to 0.4-112 ppm of MMA (8-h TWA) complained of frequent cough and sputa and 4 of throat irritation. All cases were related to the high exposure group (exposures between 5 and 112 ppm) (Mizunuma et al., 1993). It is however not reported in this paper, if short-term high exposure levels beyond 100 ppm were observed in this work force.”

Comments on the reliability of the Mizunuma study

In all the worker health studies that reported 8hr time weighted average exposure data, peak (short term exposures) were considerably higher. The confounding effects of direct irritation on the respiratory tract cannot be excluded and therefore the study cannot be taken as evidence of asthma caused by MMA.

Conclusion on the reliability of the Mizunuma study

Overall it is concluded that the study of Mizunuma is of low reliability and unsuitable for use in a WoE assessment.

9.2.3 Pickering et al., 1993

The independent chest physician Professor Pickering was invited as an independent chest physician to conduct a study on a cohort of MMA-exposed workers in a manufacturing facility in the UK dedicated to the production of PMMA-cast sheet and MMA-based composites. Confidential exposure data pertaining to these workers and this facility was provided to the EU for risk assessment for MMA to assist in their review.

The EU and OECD Risk Assessments describe this study as follows: *“Pickering et al. of the North West Lung Centre, Manchester, UK conducted 2 studies on workers involved in the manufacture of polyMMA acrylic sheet and liquid MMA composites at the ICI Acrylics sites at Darwen in the UK (ICI, 1993 – reported as Pickering et al., 1993). Worker turnover at the sites was reported by ICI to be low and exposure to MMA as high as 100 ppm (8 h TWA) in the past years. The first study was a cross-sectional study involving 384 (89.1 %) of a total workforce of 412 and consisted of an assessment of lung function (using simple spirometry to measure FEV₁ and FVC) and a health questionnaire. The second study was a follow-up on those individuals not available for the first study, a population of past leavers and those workers identified as having 2 or more work related respiratory symptoms in the first study.*

In the first study 1 individual was identified by the authors to have a medical history and peak expiratory flow measurements which are suggestive of occupational asthma. A number of individuals in the study reported symptoms of irritation to the eyes and respiratory system particularly following high, transient exposure to MMA.

In the second study (Pickering et al., 1993) no evidence of respiratory sensitization was observed in the remainder of the current workforce. From a total past leaver population of 140 individuals, 83 (59.3 %) participated in the follow-up which represented 80 % of the available target population. These individuals were investigated by means of a respiratory health questionnaire and spirometry measurements. Based on these data the past leavers population showed work related respiratory symptoms similar to those observed for the current working population in the first study. One individual in the population of leavers

was judged by the authors to have been respiratory sensitized to MMA. However, the clinical symptoms reported for this individual indicate the development of pneumonia followed by exposure to a respiratory irritant which could have acted as a provocation to a predisposed condition. 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”.

Comments on the reliability of the Pickering study 1993

The workforce targeted by the independent leading chest physician, Dr Pickering, was that of cast acrylic sheet workers. This workforce is extremely relevant as it has almost exclusive exposure to high concentrations of MMA which historically has been reported to be higher than the current OEL of 50ppm, but also still retains peak high exposures. The study conduct was to best clinical practices and the high level of participation ensured capture of not only current employees, but also past workers that possibly may have left due to illness. Dr Pickering judged that one individual in the population of leavers to have been respiratory sensitised to MMA. However, the OECD and EU RAR reviewers concluded that the clinical symptoms reported for this individual indicated the development of pneumonia followed by exposure to a respiratory irritant which could have acted to provoke a predisposed condition.

Conclusion on the reliability of the Pickering study 1993

It is concluded that the study of Pickering is of high reliability and quality and is suitable for use in a WoE assessment. Expert review of the publication by the UK HSE and DECOS (1995) and the OECD and EU RAR, as well as US California EPA and Canada during their reviews on MMA concluded that the study of Pickering did not constitute *“convincing evidence that MMA is acting as a respiratory sensitizer, however, there is clear evidence of acute respiratory irritation, at high exposure levels”.*

9.2.4 Wittczak et al., 1996

Wittczak and coworkers reported a case study of a 44-year-old, female secretary who had a 2-year history of rhinorrhea, dyspnea, and coughing attacks that occurred 15-20 minutes after making photocopies using xerographic toner containing “polystyrene-n-butyl methacrylate, polystyrene-n-butyl acrylate, etc.” The patient reported only work-related symptoms. Physical examination and routine laboratory tests were normal. Total IgE was “low” (18.04 ku/L) and SPT (common allergens) results were negative. NSIC (histamine inhalation challenge) showed bronchial hyperreactivity. Spirometry and PEFr were not reported. SIC was positive after 18 minutes of photocopying (FEV fell 24% at 1 hour) and after exposure (duration not described) to “thermally activated (80°C) MMA” (FEV fell 30% at 1 hour), but negative after exposure to thermally activated polystyrene. Nasal lavage eosinophils increased 24 hours after photocopying and “thermally activated (80°C) MMA.”

Comments on the reliability of the Wittczak study

The case study is reported as being that of an office worker exposed to xerographic toner containing “polystyrene-n-butyl methacrylate, polystyrene-n-butyl acrylate, etc.”. The authors apparently do not distinguish between MMA and other methacrylates/acrylates etc. and, as the product did not contain MMA, the claim of MMA causing asthma cannot be substantiated. Furthermore, heating liquid MMA to 80°C would significantly increase the

vapour pressure above that at ambient level which has in other studies already been shown to give a positive SIC responses in an asthmatics.

Conclusions on the reliability of the Wittczak study

Overall it is concluded that the study of Wittczak is of low reliability and unsuitable for use in a WoE assessment.

9.2.5 Vallieres et al., 1977

The case report describes a spray painter who reported progressive rhinitis and asthma claimed to have started one month after commencing to work with a paint containing 93% MMA, 1.4% dimethyl ethanolamine (DMEA), 0.6% 1,4-dioxane, and small amounts of pigment. SIC testing was performed by spraying a liter of test liquid in a "small, poorly ventilated room" over 13-14 minutes; air levels were not measured. SIC was positive with paint (FEV1 fell 29% immediately, and 23% at 8 hours) and with a 2% aqueous solution of DMEA (FEV fell 58% immediately, and 27% at 8 hours). By contrast, SIC was negative with 100% MMA and with a 0.6% aqueous solution of 1,4-dioxane. Skin prick tests with "high concentrations" of DMEA caused similar wheal-and-flare response in the case subject and three unexposed controls, suggesting an "irritative effect."

Comments on the reliability of the Vallieres study

The case study appears to be a "classic" asthmatic response to a product containing MMA, but in the absence of a positive SIC with 100% MMA it is conclusively shown that it was actually not related to MMA at all. Moreover, although the SIC response to DMEA suggested a sensitizer-induced response, there are no other reports of DMEA-induced allergy. The strong irritating capacity of DMEA, however, is well recognised (Klonne et al., 1987; Leung and Blaszcak, 1998; Smyth et al., 1951). And despite a relatively low vapor pressure (4 mm Hg at 20°C; New Jersey Department of Health, 2010), sufficiently high air concentrations of DMEA would be expected after spraying a liter of product in a small, closed space as to elicit an irritant provoked asthma attack.

Conclusions on the reliability of the Vallieres study

Overall it is concluded that the study of Vallieres is of low reliability and unsuitable for use in a WoE assessment.

9.2.6 Reynaud-Gaubert et al., 1991

Reynaud-Gaubert and coworkers (1991) reported the case study of a 39-year old orthopedic theater nurse developed breathing difficulties during the course of mixing cement to seal prostheses. She had previously complained of rhinitis, conjunctivitis and a spasmodic "cold". Spirometry and chest X-rays were normal. Provocative exposure to the MMA-containing cement resulted in a fall of 25% in VEMS within 30 minutes of exposure. Respiration returned to normal following the application of b-2-mimetics. Bronchial reaction to acetylcholine was positive, typical of an asthmatic subject.

Comments on the reliability of the Reynaud-Gaubert study

From the publication of Pickering 1986 it is evident that exposure to high levels of MMA (374 ppm observed during the first 2 minutes) can occur when bone cement is mixed on an

open trolley and this is likely that this individual would also be routinely exposed to very high concentrations of MMA. Consequently it is likely that **confounding effects of direct irritation on the respiratory tract were extremely likely if not unavoidable**. On the available information there is no evidence that MMA caused the development of asthma but clear evidence that high levels of MMA vapour could trigger an asthma attack in an individual that may have developed asthma due to some other reason. The EU RAR reviewed this case study and concurred with this interpretation when they concluded *“It is therefore considered that it cannot be concluded that MMA was acting other than in an irritant and non-specific manner”*.

Conclusion on the reliability of the Reynaud-Gaubert study

Overall it is concluded that the study of Reynaud-Gaubert low reliability and although suitable for use in a WoE assessment it is of weak strength as causation is not supported by quantitative evidence linking MMA with the development (causation) of asthma.

9.3 Exposure Profile

9.3.1 Introduction on identified uses in the CLH report

The substance has several uses which include adhesive and sealants, as a monomer for polymerisation or intermediate in synthesis of other chemicals, manufacturing of acrylic sheets, in the manufacture of resins. Consumers may be exposed via adhesives and sealants, machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners.

This substance is used by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

9.3.2 Comments on identified consumer uses in the CLH report and on ECHA homepage

Fragrances and air refresheners

The CLH report states "*Consumers may be exposed via ... fragrances and air fresheners.*"

We would like outline that we are not aware of any use of MMA in fragrances although MMA is listed as flavouring agent in EU Regulation 1334/2008. Moreover, due to the strong, pungent odour of MMA, which is perceived as unpleasant at higher concentrations, it is very unlikely that relevant concentrations of liquid MMA are used in consumer products. The same applies for air refreshing products. In the EU Risk Assessment (ECB, 2002) the odour threshold of MMA is listed in a range of 0.21-1.4 mg/m³ (0.05 - 0.34 ppm). Amoore and Hautala (1983) report the odour detection threshold for MMA at 0.083 ppm (0.34 mg/m³)

Adhesives

A very small fraction (< 0,1%) of the MMA production/import is used in specialized 1- or 2-component adhesives and cements in the do-it-yourself market. For this application, small amounts are used at each time, relevant routes of exposure are inhalation and dermal exposure. Potentially relevant endpoints are respiratory irritation, skin irritation and skin sensitisation.

ECETOC TRA has been used to determine the safety of the use. While the model assumes a time window of 4 h, the reactive 1- or 2-component systems actually polymerise within 5-10 minutes and start to harden after less than 5 minutes. By reducing the diffusion of free monomer (MMA), the beginning polymerisation process progressively limits the emission of MMA from the moment the polymerisation has been started and effectively stops it once the product is cured.

Dermal exposure is minimized (if not prevented entirely) by using tubes and sticks to mix and apply the product.

Information on release to the environment

According to ECHA homepage, "*other release to the environment of this substance is likely to occur from: indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners) and outdoor use.*"

With exception of the unlikely use as fragrance composite (see above) and in adhesives, the brief description above indicates these are all polymer uses. There is no free MMA present in such products. Depending on the production process of the polymer a small fraction of residual monomer may be dissolved in the polymer. Exposure of consumers and the environment to the residual monomer is limited by the small quantities as well as by the slow diffusion. No toxicologically relevant exposure is expected during these types of use.

9.3.3 Article service life

“Other release to the environment of this substance is likely to occur from: outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials), indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment), indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners) and outdoor use. This substance can be found in complex articles, with no release intended: electrical batteries and accumulators, vehicles and machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines). This substance can be found in products with material based on: leather (e.g. gloves, shoes, purses, furniture), plastic (e.g. food packaging and storage, toys, mobile phones), fabrics, textiles and apparel (e.g. clothing, mattress, curtains or carpets, textile toys), paper (e.g. tissues, feminine hygiene products, nappies, books, magazines, wallpaper), rubber (e.g. tyres, shoes, toys), stone, plaster, cement, glass or ceramic (e.g. dishes, pots/pans, food storage containers, construction and isolation material), metal (e.g. cutlery, pots, toys, jewellery) and wood (e.g. floors, furniture, toys).” (ECHA homepage)

Remark

For this range of products, the same remark applies as above: There is practically no free MMA present. Depending on the production process of the polymer a small fraction of residual monomer may be dissolved in the polymer. Exposure of consumers and the environment to the residual monomer is limited by the small quantities as well as by the slow diffusion. No toxicologically relevant exposure is expected during these types of use.

9.3.4 Widespread uses by professional workers

“This substance is used in the following products: polymers, coating products, inks and toners, fillers, putties, plasters, modelling clay, laboratory chemicals and water treatment chemicals. This substance is used in the following areas: building & construction work, printing and recorded media reproduction, scientific research and development and municipal supply (e.g. electricity, steam, gas, water) and sewage treatment. This substance is used for the manufacture of: plastic products. “ (ECHA homepage)

Remark

For the professional sector the text from MMA summary on the web does not allow to identify the uses with a relevant potential for exposure. Most of them are polymer uses where MMA is no longer present. In a small number of professional applications free monomer (MMA) is used and polymerized in situ. Case studies in which MMA is has been associated with asthma tend to come from some of these applications.

In the Chemical Safety Assessment these uses have been assessed in ES11 (Exposure scenario 11: Professional end use in formulations). For most of them a comprehensive exposure analysis has been performed in the context of the EU Risk Assessment (ECB 2002).

Plastics workshops: Use of reactive adhesives containing MMA	Reactive cements based on MMA, polymer and a polymerization initiator are used to bond PMMA (acrylic) sheets, e.g. for aquaria or transparent machine covers
Dental industry: Manufacture of prosthetic orthodontics/ dentures (laboratory)	Formulations containing MMA are mixed and polymerized to build and repair dentures
Medical/ surgery industry: Bone cement e.g. for hip replacements (hospital)	Orthopaedics use formulations containing MMA to bond e.g. hip implants with the bone. This medical device application is outside of the scope of REACH and hence, not part of the registration. It is mentioned here, because it is nevertheless a pertinent use in this context.
Building industry: Reactive floor coating	A polymerizing mixture containing MMA, other co-monomers, polymer, a mineral filler (e.g. sand) and an initiator (e.g. dibenzoylperoxide) is spread with a wiper to create a robust, seamless floor coating e.g. for factory and storage buildings and cold storage.
Building industry: Roadmarking	A polymerizing mixture containing MMA, other co-monomers, polymer, a mineral filler, light-reflecting beads, pigments and an initiator (e.g. dibenzoylperoxide) is applied to the road surface.

For these applications, relevant routes of exposure are inhalation and dermal exposure. Potentially relevant endpoints are respiratory irritation, skin irritation and skin sensitisation. In most cases, except roadmarking (outdoor), inhalative exposure is controlled by general or local ventilation.

9.3.4.1 Detailed exposure analysis

The text of following sections consists mostly of material presented in the EU-RA (ECB 2002). In general, the format of EU-RA can be understood from many perspectives as precursor of the current REACH dossiers.

Especially with respect to the information on job sectors which are not considered under REACH, the EU-RA represents a highly valuable source of information when it comes to CLH discussions with human data outside the scope of REACH. For MMA and this CLH report, this is true for the medical and cosmetic sector where cases were identified in the RNV3P database.

Use Area: Plastics workshops: Use of reactive adhesives containing MMA (EU-RA: *Use of adhesives in the further processing industry*)

Size of the exposed cohort: There is no definitive number available for the size of the exposed cohort. The companies involved are mainly SMEs. A rough estimate is that the number is somewhat, but not an order of magnitude smaller than the number of dental technicians (see details below).

MMA is used in reactive adhesive preparations (one- and two-package polymerisation adhesives) which are used in the industrial area and for skilled trade applications being a potential source of

exposure (Franck, 1988; Habenicht, 1986). The quantity of MMA is only known for a 2-package polymerisation adhesive used in the automotive industry. One component contains 60% MMA.

Structural MMA adhesives (sometimes called “MMA’s”) involve methyl methacrylate co-polymer resins and initiator systems, or resin polymers and hardeners. Liquid MMA can be the main part of a multi component formulation (up to 70%) and is partially polymerised to form a paste. Additional monomers, amines, rubbers, fillers make up the rest of the formulation. These adhesives are generally cured using a second stage peroxide type initiators and used for bonding in marine and automotive sectors.

MMA containing adhesives are applied in many different branches like plastics industry, automotive industry, electric industry, wood processing and shoe manufacturing. In the field of engineering, device and tool construction industries, anaerobic and photocuring adhesives are used to bond metals or metal and glass during assembly. Automatic or semi-automatic bonding machines are employed within continuous production processes (production lines). After the bonding step, the workpiece is hardened by UV light within closed systems. Afterwards the components which are still warm, are in some cases stored in open systems, so that residual gases could evaporate into the workplace atmosphere.

Workplace measurements: MMA exposures during application of adhesives at workplaces belonging to different industries (adapted from EU RA; ECB 2002)

Work area / activities	Year of measurements	Number of measurements	Exhaust ventilation	Range of measurement data [mg/m ³]	Mean value [mg/m ³]	95 th percentile [mg/m ³]	Source
- Adhesives	1992	--		8.3 – 13.1	11.1	--	CEFIC, 1995*
Bonding e.g. plastics industry, electric industry, shoe manufacture	1990 – 1995	106 34	no yes	--	11 3	132 83	BGAA, 1995

*) calculated from ppm to mg/m³ (factor 4.16)

For the use of adhesives, 8-h TWA values in the range of 8.3 to 13.1 mg/m³ (2 – 3.2 ml/m³) were reported with short-term values up to 135 mg/m³ (33 ml/m³; 120 min) for a different application (CEFIC, 1995). During bonding metallic stripes, lower exposures were observed (confidential information).

Measurement results obtained in different industries were provided from the German workers compensation funds (see table above), mainly from plastics industry, e.g. bonding of acrylic sheet, and also electric industry and manufacturing of shoes, in total 70 companies. During bonding small areas (electric industry, manufacturing of shoes), exposure levels were located <11 mg/m³ (2.6 ml/m³, 50th percentile) for workplaces without LEV and <3 mg/m³ (0.7 ml/m³, 50th percentile) for workplaces equipped with LEV. The corresponding 95th percentile amount to 132 mg/m³ (32 ml/m³, without LEV) and 83 mg/m³ (20 ml/m³, with LEV), respectively. Exposure levels higher than the 90th percentile of 80 mg/m³ (19.2 ml/m³) without LEV and 46 mg/m³ (20 ml/m³) with LEV were observed when large areas were bonded. It is stated, that exposure levels are in the area of 11 mg/m³ (2.6 ml/m³, 50th percentile, see above) when small areas are bonded. Short-term exposure levels lie in the area of 195 mg/m³ (46.9 ml/m³).

In the case of handling adhesives, frequent immediate skin contact has to be taken into consideration. Generally workers only avoid immediate skin contact with adhesives that can be removed only with difficulties. But the corresponding adhesives harden only slowly on the skin. Possibly, these adhesives are removed later with the aid of skin cleaning agents which are also employed following contact with paints and thus have the opportunity to penetrate the skin. Dermal exposure as a result of drumming or handling adhesives has to be taken into account (Kliemt, 1995). The corresponding exposure level is assessed by the EASE model.

The RNV3P database did not include any asthma case reports associated with adhesive uses with MMA.

Use Area: Dental laboratory: Manufacture of dentures (EU-RA: Orthopaedic workshops, dental laboratories and surgeries)

Size of the exposed cohort: Our survey indicated that there have been approx. 18.800 dental technicians in France (UNPPD, 2013). EU census data collected by Kimber and Pemberton (1914) listed approx. 150.000 dental technicians in the EWR at about the same time.

In dental laboratories and in dental surgeries liquid MMA (assumed 80%) and powdery MMA prepolymers are used inter alia to construct orthodontic components, fillings¹ and inlays. Use of MMA can also be assumed for orthopaedic workshops. Exposure relevant activities like filling, dosing, mixing, bonding and humidifying with liquid MMA (see below) may be performed on different time scales as several times for a short duration or regularly over a longer period of time, possibly over the whole shift. It may be assumed that suitable ventilation equipment is not always employed.

Typically, a dentist will make an impression of the patient's mouth / teeth (alginates or polyvinylsiloxane) at the dental surgery. Then the impression is sent to a dental laboratory, where dental technicians use gypsum/ plaster, alginates and wax to create a new master mold for the patient's mouth/teeth impression. The final dental dough mixture is prepared by mixing the dry powder ingredients with the liquid methacrylate (e.g. MMA, bis GMA, other dimethacrylate monomers) and heated in the prepared dental mold. These types of dental activities are recommended to be carried out with local extraction and ventilation (LEV).

After curing the dental mold is ground, milled and machine polished by dental technicians to make it smooth. Other identified exposures to dental technicians examined in the literature include inhalation of micron sized silicas, resin particulates and metal amalgam substances from the powder mixing and dental prosthetic polishing operations. New processes based on 3D printing are in development in order to produce replacement teeth (MMA is not used directly as too volatile and not reactive enough).

While MMA monomer is used in dental mixtures, many other chemicals are additionally used in this job scenario including: alternative methacrylate monomers (e.g. bisGMA, other dimethacrylate monomers), metals, dental adhesives. Besides the potential for exposure to these substances exposures to powders and polymeric dusts may occur during the grinding, milling, and polishing operations in this sector.

¹ MMA is not used in dental fillings. It is unsuitable for that purpose, because the polymer is much denser than the monomer and shrinks during polymerisation

Measurement results obtained in dental laboratories are provided (German federal monitoring authorities and the German workers compensation fund provided by the producers). Exposure data (n = 112) from 1990 – 1995 have been provided for the coating with casting resins, lacquers and paints (German workers compensation funds). At present it is not possible to differentiate the data further. It is stated that exposure levels during the use of paints and lacquers are near the detection limit and during the use of casting resins e.g. for orthopaedic purposes are near 187 mg/m³ (45 ml/m³) without LEV and 61 mg/m³ (14.7 ml/m³) with LEV, which is the 95th percentile for all activities (painting and use of resins).

Exposures in dental laboratories and surgeries at workplaces with local exhaust ventilation are usually between 3 and 6 mg/m³ (0.7-1.4 ml/m³) (data from the German workers compensation fund in 1990 – 1994). From the federal monitoring authorities single exposure levels in dental surgeries of <62 mg/m³ (15 ml/m³), 7.5 mg/m³ (1.8 ml/m³) and “not detected” are provided. According to the federal monitoring authority Hamburg the short-term values at workplaces with suitable LEV are below 42 mg/m³ (10 ml/m³).

Exposures of 197.5 mg/m³ (47 ml/m³), 155 mg/m³ (37 ml/m³) and 125 mg/m³ (30 ml/m³) for some hours without LEV (federal monitoring authorities) and shift averages of 110 mg/m³ (26.4 ml/m³) and 14 mg/m³ (3.4 ml/m³) under unfavourable conditions (small room, no ventilation, workers compensation fund) have been observed. Short-term exposures (30 min, n = 4) up to 144 mg/m³ (35 ml/m³) without LEV and 600 mg/m³ (144.2 ml/m³) under unsuitable ventilation conditions have been measured. The federal monitoring authority Hamburg shows significant differences depending on the use of LEV. Especially during a specific task (alternately humidifying orthodontic components with liquid MMA and strewing with powdery prepolymerised MMA) the short-term values (5 min) measured at workplaces without LEV in six laboratories were between 420 – 840 mg/m³ (100 – 200 ml/m³) or sometimes even higher (FID measurement 1989/90).

Dermal exposure has to be considered during filling, mixing and coating activities, which are assumed to be performed repeatedly on a daily basis.

Use Area: Medical device: Bone cement e.g. for hip replacements (EU-RA: Medical application of casting resins)

Size of the exposed cohort: There is no definitive number available for the size of the exposed cohort (orthopedic theater sisters and surgeons). Our rough estimate is that the number is by order of magnitude comparable to the number of dental technicians (see details above).

MMA is employed medically as a component of bone cement (mixture of MMA and its polymer) for orthopaedic purposes and for fixing metal and plastic prostheses. Short-term inhalation exposure (a few minutes during an operation) is possible when these cements are prepared for application. It can be assumed that during medical applications protective gloves will be employed for reasons of medical hygiene. In assessing the dermal exposure, it has to be borne in mind that the producers recommend gloves which provides only limited protection. Therefore, the EASE model is applied to calculate dermal exposure levels.

In a study regarding the exposure of hospital operating personnel during operations where MMA was used in surgery only in 4 of 27 cases MMA concentrations above the detection limit (1.2 mg/m³ = 0.29 ml/m³) were found (3.7; 4.0; 4.0; 55.3 mg/m³ = 0.9; 1.0; 1.0; 13.3 ml/m³; Sass-Kortsak et al., 1992). Darre et al. (1992) reported workplace concentrations between 210 and 420 mg/m³ (50 –

100 ml/m³) of MMA during hip and knee replacement operations under conventional operating conditions without laminar airflow. Measurements were made in the breathing zone of the surgeons. The concentrations remained at the measured levels for a maximum of 10 minutes.

Use Area: Building industry: Reactive floor coating (EU-RA: Use of MMA containing floor coatings in skilled trade sectors)

Size of the exposed cohort: There is no definitive number available for the size of the exposed cohort. In Germany, for example, about 400 SMEs share the reactive floor coating market, about half of them (also) use acrylic systems among others (Epoxy and PU). Our rough estimate is that the number of workers using acrylic floor coatings is 10-20 % the size of the number of dental technicians (see details above).

Reactive flooring / concrete coating systems normally contain between 20 - 40% wt of liquid MMA with other ingredients such as solid co-polymer resin powder, fillers (silicas), initiators (Benzoyl peroxide), waxes and accelerators (N,N-dimethyl-p-toluidine). The process of preparation involves mixing the dry powder ingredients together into the liquid MMA and then adding the initiator at the last stage to enable curing to begin just before layering the mixture onto the floor surface.

One important open application of reactive resins is floor coatings. Preparations containing up to 20% MMA are used by specialised companies. The applied mixture is polymerised within approx. 30 – 60 min dependent on temperature and initiator concentration. However, a certain amount of MMA may evaporate from the reaction mixture before it is fully polymerised. The evaporation of MMA is reduced to a certain extent by a cover layer of paraffin forming a film on the surface of the coating.

In the CEFIC data collection (CEFIC, 1995, see below table) only a limited number of data were available: 8-h TWA of 125 – 424 mg/m³ (30–102 ml/m³) and short-term exposure up to 832 mg/m³ (200 ml/m³).

Table Concentration of MMA in air at the workplace, uses of reactive resins during coating works

Work area / activities	Year of measurements	Number of measurements	Exhaust ventilation	Mean value * (no TWA) [mg/m ³]	Mean 8-h TWA [mg/m ³]	95 th percentile [mg/m ³]	Source
Floor coating	1990 1993	3 4	-- --		399 204	-- --	CEFIC, 1995 **
- Priming	--	4 3	no yes	605 196		--	Kersting et al, 1995, German BIA/BAU-BG
- Mixing	--	16	no	715		--	
		4	yes	381		--	
		20	outside	174		--	
- Transport	--	15	no	615		--	
- Covering	--	47	no	610		--	
		13	yes	601		--	
- Sealing	--	40 10	no yes	687 774		--	
Floor coating	1990 – 1995	78 34	no yes	--	241*** 141***	1045 625	BGAA, 1995

* Exposure duration not known

** Calculated from ppm to mg/m³ (factor 4.16)

*** 50th percentile of the measurement collective

Data provided from the German workers compensation funds were obtained mainly within the production of industry floors (see Table 4.4, BGAA). During floor coating high exposure levels were observed: the mean 50th percentile amounts to 241 mg/m³ without LEV (51 ml/m³, n = 78 within 7 enterprises) and 141 mg/m³ with LEV (34 ml/m³, n=34 within 2 enterprises). The corresponding 95th percentile are 1,045 mg/m³ (251 ml/m³, without LEV) and 625 mg/m³ (152 ml/m³ with LEV). It is stated that exhaust ventilation is rather seldom applied. The 95th percentile of short-term exposures (<1h) of 683 mg/m³ (164 ml/m³; n = 50) was measured during floor coating.

Additional measurements were provided (Bau-BG, 1993, available through German GISBAU (information system of Bau-BG)) and recently published (Kersting et al., 1995, see Table 4.4). Data available from this project indicate that without technical and organisational measures the occupational exposure concentrations vary considerably and high exposures (up to 774 mg/m³ (186 ml/m³)) have been observed at several occasions.

In the area which, in part, belongs to the building trade, it has to be considered that gloves possibly are not worn and that dermal exposure occurs not daily.

Technical measures may reduce exposure to MMA. Kersting et al. (1995) and Christensen (1990) presented evidence that suitable ventilation and accompanying reorganisation of working methods ("working in line") may significantly reduce MMA exposure below 210 mg/m³ (50 ml/m³) and possibly to mean values of <20 mg/m³ (<5 ml/m³).

A method of personal protection to reduce occupational exposure is the use of an "airstream helmet" where filtered air is pumped into the breathing zone. With this method also a significant reduction of exposure to values below 40 mg/m³ (10 ml/m³) may be obtained in areas with high MMA concentrations (Kersting et al., 1995).

Additional uses of MMA in polymer concrete and in road marking materials are mentioned by the producers. It is assumed that the exposures are in the same range or even lower than observed for floor coating works.

Building industry: Roadmarking

Size of the exposed cohort: There is no definitive number available for the size of the exposed cohort. This is a highly specialised work area with a small number of companies. Our rough estimate is that the number of workers in the roadmarking sector is comparable to the floor coating sector above.

Road marking applications include MMA as part of the binding mixture (between 20-40% wt) along with other methacrylates/acrylates, resin polymers, initiators and coloured pigments. The mixture once prepared is immediately painted onto the road surface and cures quickly (between 30 to 60 minutes). The evaporation of MMA is reduced to some extent by wax in the formulation creating a film surface on the coating.

This is a relatively new application of methacrylic resins therefore no exposure survey exists in the old risk assessment. The CSA predicts exposures in this work area are below the DNEL and this has been confirmed by control measurements.

Because the application point of the machine directly above the road is relatively far away from the breathing zone exposures are safely lower than the OEL/DNEL.

Use of MMA in cosmetics

Size of the exposed cohort: At this time, there are no exact numbers available from Europe. In the US 62,000 manicurist and pedicurists were registered in 2013 (Kimber and Pemberton, 2014). It can be assumed that today the numbers are similar in Europe.

For this area no in-depth analysis is available, because in the chemical safety assessment it became apparent early on that, because MMA is a potential skin sensitiser, from a REACH perspective there was not enough information available to describe safe work procedures. For that reason, this area has been designated as a “use advised against” and has been excluded from the registration.

Moreover, DIY products would be excluded from the scope of REACH because they fall under the cosmetics legislation.

Cosmetic nail products used for beautification include nail polish, artificial nails, and nail polish remover. Nail polish generally includes three types: basecoat, pigmented nail polish, and aftercoat. Artificial nails include preformed plastic nails, sculptured nails, and gel nails. Nail polish remover is often an organic solvent with added scents and colors. Products used in the cosmetic nail industry use a diversity of chemicals with methacrylate chemistry being used primarily in the artificial nail segment. As mentioned earlier and in Appendix 9.4.4, the EU registrants of MMA have intentionally considered use in nail sculpting a “use advised against” due to safety concerns from skin sensitization. Consistent with this concern MMA monomer as an ingredient in artificial nails was banned in 1974 in the United States (Engasser et al., 2000) and products with high levels of MMA were recalled in Europe. Due to these restrictions and understanding, MMA monomer use in cosmetic nails is expected to be minimal and has been substituted by other methacrylate monomers. However, an exposure to MMA cannot be excluded in case of violations of the REACH regulations. The polymerized form of methyl methacrylate, PMMA, is used routinely is considered to be of low hazard potential. It is not uncommon for products to be incorrectly labelled as the monomer instead of polymeric form. Besides methacrylates, other chemicals used in the cosmetic nail sector at significant levels include cyanoacrylate, formaldehyde, toluene, N-Methyl-2-pyrrolidone, and phthalates. Most of these are well characterized respiratory irritants and has the potential to provoke asthma-like symptoms.

The CLH proposal for harmonized classification and labelling references nine case reports involving nail applications from the RNV3P database where a high to moderate level of attributability to MMA has been considered for respiratory sensitization. This attributability lacks plausibility considering the acknowledgement by healthcare professionals in the RNV3P network that they “*use the occupational disease table No. 82 (TG 82) “Disorders caused by methyl methacrylate” for cases involving exposure to (meth)acrylates other than MMA*” (ANSES, 2017).

If respiratory sensitization occurs in this occupation it is not well characterized and likely of low occurrence. The strength of evidence for occupational asthma caused by MMA is very weak based upon its minimal use, known misclassification of MMA within the RNV3P database, and higher exposure potential to a number of chemicals in this sector with known respiratory irritating properties capable of provoking asthma-like symptoms.

Except for a few measurements in single publications there is no general exposure analysis available for this area. Due to the nature of the products and the work conditions it can be assumed that the general exposure conditions for cosmeticians are similar to those of dental technicians or orthopaedic sisters.

Use of MMA in the printing sector

The printing product sector for UV cure inks products is generally manufactured within industrial type processes and the end product is supplied in sealed units to the end user. The most popular printing techniques that use UV ink are flexography and screen printing. A typical UV ink consists of monomer and/or oligomer, pigments, photoinitiators, and other additives. The ink coating applied by the appropriate method is polymerised or cured by exposure to UV rays. When the photoinitiators are exposed to UV light, the oligomers and monomers cross-link or polymerise. The monomers used are highly functional reactive materials and include unsaturated polyester/acrylated polyesters; acrylated epoxy resins; acrylated urethanes (both aliphatic and aromatic; acrylated silicone resins; acrylated polyethers; acrylated melamines; acrylated oils; N-vinyl urethanes and thiolene systems.

MMA is not sufficiently reactive to be of use with this technology. Hence, we are not aware of liquid MMA being specifically used within standard UV cure printing inks. There are formulations which incorporate solid PMMA (co-)polymer products but these are not liquid MMA. Therefore, MMA vapour is not expected to be released from these types of processes and products.

In conclusion, it is not plausible that asthma cases attributed to MMA are actually due to exposure to MMA.

Optical (eyewear)

While the RNV3P database did not include any asthma case reports associated with optical uses with MMA, the CLH document mentions other applications of MMA such as optical eyewear whereby there have been causes of occupational asthma cited. Investigation of the published literature did indeed find a reference to "Occupational asthma caused by acrylates in optical laboratory technicians" published from the "Journal of investigational allergology & clinical immunology 2011: 78-9" by Quirce et al. In the document it is claimed that two patients developed occupational asthma and rhinitis caused by 'methacrylate' contained in organic eyeglass lenses as confirmed by SIC tests. Patient 1 was involved in grinding and polishing PolyMethyl methacrylate (PMM) eyeglasses made of Polycarbonate and PMM and the second patient had PMMA eyeglasses introduced in her workplace 15 years previously.

It is our assertion that the bronchial hypersensitivity and inhalation effects were more likely caused due to the polymeric dust from the grinding and polishing activities.

The use of liquid MMA for eyewear is not known. Eyewear components, such as spectacle frames, are typically injection moulded from other polymer pellets. Spectacle lenses can be manufactured from solid polymer (PMMA) blanks and machine finished, which could result in workers being exposed to the dust generated from the grinding and polishing activity.

Plastics (polystyrene)

The CLH document references 3 cases from the RNV3P database (Case report #28, 29, 30) of occupational asthma attributed to MMA from the Polystyrene (PS) industry for two machine operators and one packer. Polystyrene and Polymethylmethacrylate (PMMA) are different polymer

resins with different material properties and raw material starting monomers. Although PS can be used in some PMMA applications, the superior UV resistance of PMMA is used for applications where the functionality of weathering and optical transparency is critical.

Styrene is polymerized in a similar polymerization process to methyl methacrylate with initiators and other co-monomers to make solid polymer products at industrial facilities. PMMA can also be blended with Polystyrene. MMA is not specifically associated with the polystyrene industry but there are polymer products in which MMA is co-polymerized with styrene /other monomers to form solid co-polymer products. All solid PS, PMMA and blended PS/PMMA products can cause polymeric dust when processed or machined.

Based on the limited case study information from the RNVP3 database, it is difficult to understand why MMA has been attributed to these cases. Without reference to more specific data it is likely that the workers have been exposed to polymeric dust, which may or may not have included solid PMMA.

9.3.5 Formulation or re-packing

This substance is used in the following products: polymers.

Release to the environment of this substance can occur from industrial use: formulation of mixtures and formulation in materials. For these applications, relevant routes of exposure are inhalation and dermal exposure.

Potentially relevant endpoints are respiratory irritation, skin irritation and skin sensitisation. The manufacturing process is performed mostly in closed systems and exposure is minimized using local exhaust ventilation.

A special case is the formulation of reactive resins because there- in contrast to all other production and formulation exercises monomer is still present during the filling/packaging processes. In the EU-RA (ECB 2002) this sector has been described as:

Production of reactive resins (incl. Dental resins, reactive and floor coatings) and adhesives

Size of the exposed cohort: There is no definitive number available for the size of the exposed cohort. It is a small, specialized workforce in this area, probably less than 1000 people in the whole of Europe.

Table Exposure to MMA in Workplace Air

Job category	Year of measurement	No. of samp.	8-h TWA Range [mg/m ³]	Mean 8-h TWA [mg/m ³]	50 th percentile [mg/m ³]	90 th percentile [mg/m ³]	Short term conc. [mg/m ³](min)
Coatings, resins ¹⁾							
Adhesives production production/packaging	1993-98	15	5 – 60 ²⁾	-	23	57	-
- Production of reactive resins (incl. Dental resins, reactive and floor coatings)	1993-98	33	1.7 – 264 ²⁾	-	28	119	-
- Production of floor coatings	1995-97	5	1.5 – 25	-	-	-	-
- Production of reactive coatings	1995-98	21	5 – 264 ²⁾	-	-	-	-
- Production of dental resins	1996-97	7	3 – 84	-	-	-	-

¹⁾ According to the producers PPE is generally worn during activities with high exposure potential

²⁾ New data from Röhm 1998

Reactive resins are prepared by mixing monomers and/or pre-polymers with fillers and other additives in closed batch processes.

The resins containing 20 – 80% MMA are used in floor coatings or other speciality resins like adhesives (e.g. glues for acrylic sheets), road markings, polymer concrete or dental and medical application.

Exposure is possible during sampling and analysis, filling and drumming, as well as during cleaning, maintenance and repair works.

According to information provided by the producers of MMA, personal monitoring data for MMA in reactive resins (incl. Dental resins, reactive and floor coatings) production range from 1.7 – 264

mg/m³ (0.4 to 63.4 ml/m³) (8-h TWA, c. f. Table 4.1) for all activities in manufacture. The 90th percentile is 119 mg/m³ (28.5 ml/m³) (Röhm, 1998).

Individual measurements during production of adhesives range from 5-60mg/m³ (1.2 – 14.4 ml/m³) (8-h TWA, c. f. Table 4.1) for activities involved in the production and packaging. The 90th percentile is 57 mg/m³ (13.8 ml/m³) (Röhm, 1998).

9.3.6 Uses at industrial sites

“This substance is used in the following products: polymers.

This substance is used in the following areas: mining, municipal supply (e.g. electricity, steam, gas, water) and sewage treatment, health services and building & construction work.

This substance is used for the manufacture of: chemicals, plastic products, electrical, electronic and optical equipment, machinery and vehicles, mineral products (e.g. plasters, cement), metals, fabricated metal products, wood and wood products and pulp, paper and paper products.

Release to the environment of this substance can occur from industrial use: for thermoplastic manufacture, as processing aid, in processing aids at industrial sites, as processing aid, of substances in closed systems with minimal release, in the production of articles and as an intermediate step in further manufacturing of another substance (use of intermediates). “ (ECHA homepage)

Remark

Potentially relevant endpoints are respiratory irritation, skin irritation and skin sensitisation. Most of the industrial use processes occur in closed systems and exposure is further minimized using local exhaust ventilation. Cast sheet production, one of the polymerization processes for the production of acrylic (PMMA) sheet is a semi-open process with a somewhat higher exposure potential. In this case dedicated ventilation equipment is used to control exposure. Because of the higher exposure potential this area will be described in more detail.

Production of cast acrylic sheet

The production process of cast acrylic sheet consists of four independent production steps with different exposure potential:

1. Production of syrup (monomer mixture containing all pigments, colourants, fillers and aids for polymerisation): The components are mixed in a batch reactor at room temperature. This production step results in a viscous pre-polymer.
2. Cell filling (syrup/pre-polymer is filled into cells consisting of two sheets of silicate glass separated by a plastic seal which determines the thickness of the acrylic sheet): In this semiautomated process the syrup is filled manually into the cells which are finally sealed and transported to the polymerisation unit. Due to the high exposure potential purpose-designed LEV is used according to the producers during this production step.
3. Polymerisation: The sealed cells are stored for several hours at increased temperature in large incubators or in a water bath.
4. Tempering: At the end of the step 3 when the polymerisation process is almost complete, the cells are slowly heated to temperatures up to or above 100 °C in order to remove most of the residual monomer by final polymerisation. The high temperature is maintained for several hours. It is needed

because the diffusion of the remaining MMA is very slow at this stage and, as a consequence, the availability for the polymerisation process would otherwise be too low. Finally, the cells are slowly cooled down to room temperature and the silicate glass sheets and the plastic seals are removed.

Table Exposure to MMA in Workplace Air

Job category	Year of measurement	No. of samp.	8-h TWA Range [mg/m ³]	Mean 8-h TWA [mg/m ³]	50 th percentile [mg/m ³]	90 th percentile [mg/m ³]	Short term conc. [mg/m ³](min)
Transesterification ^{1),2)}							
- Filling / production	1993-98	36	0.0 – 55 ²⁾	-	2.1	10	-
	1993-94	48	0.4 – 84	9.2	-	-	-
	1993-94	14	-	-	-	-	33 (5 min)
Cast sheet production ^{1),2)}							
- All activities	1990-93	21	0.8 – 225	-	-	-	
	1992-93	15	1.4 – 62	-	-	-	
	1993	2		-	-	-	121 – 749 (15 min)
	1992-93	5		-	-	-	23 – 233 (7-15 min)
- Cast production	1993	-	2.1 – 686	92	-	-	-
	1993-94	21	4.2 – 50	21	-	-	-
	1993-94	26	25 – 112	67	-	-	-
	1993-94	22	37 – 141	91.5	-	-	-
	1993-94	19	33 – 283	146	-	-	-
	1993-94	163	-	-	-	-	75 – 412 (5 min)
- Cast filling / assembly	1993-98	127	2,3 – 714 ²⁾	-	48	148.5	-
- Syrup production	1993-98	119	2.1 – 618 ²⁾	-	42	106	-
- Waste handling	1995-97	7	1.1 – 147 ²⁾	-	-	-	-

¹⁾ According to the producers PPE is generally worn during activities with high exposure potential

²⁾ New data from Röhm 1998

Step 1 and especially 2 are the steps with the highest exposure potential during the production process. They are performed at room temperature. For activities with a high exposure potential PPE is used. Step 3 and 4 are performed at increased temperature but they have only a low potential because the containment (cells) is not breached until the polymerisation process is complete (Röhm, 1998).

According to new information provided by Röhm (1998), personal monitoring data for the single process steps involved in cast sheet production (cast filling, assembly, syrup production and waste handling) exposure values (8-h TWA, cf. Table 4.1) range from 1.1 – 714 mg/m³ (0.3 - 172 ml/m³). The 90th percentile is 148.5 mg/m³ (35.7 ml/m³). Short-term measurements of this time range were not available.

Older single full-shift measurements range from 0.8 to 686 mg/m³ (0.2 – 165 ml/ m³) with peak exposures (short-term PPE measurements) up to 750 mg/m³ (180 ml/ m³, 15 min) (cf. Table 4.1) (CEFIC, 1995).

About 190 employees were reported to be exposed in this production process (Röhm, 1998). For activities with a high probability of exposure personal protective equipment is used.

9.3.7 Manufacture

Release to the environment of this substance can occur from industrial use: manufacturing of the substance, in processing aids at industrial sites, in the production of articles, as an intermediate step in further manufacturing of another substance (use of intermediates), as processing aid, for thermoplastic manufacture, as processing aid and of substances in closed systems with minimal release.

Manufacture of MMA is performed in dedicated, closed systems in continuous processes with minimal exposure potential. Because of the low exposure potential this area is of limited interest in this analysis.

9.3.8 Summary of the Exposure Profile

This analysis focusses primarily on the use areas with open uses of MMA. Generally they tend to have a higher exposure potential than most of the industrial work processes.

In Europe about half a million workers are working in this use areas of MMA, the majority in the professional (skilled trade) field.

A more detailed assessment can be made for the prevalence of potential asthma cases in the dental sector in France: For dental technicians, a total prevalence of 0.07% for potential occupational asthma in France can be calculated considering 14 cases in the RNV3P database over 16 years of existence and approx. 18.800 dental technicians in France (UNPPD, 2013). The comparable prevalence ratio for dental assistants in France is a magnitude lower (0.005%; approx. 20.000 employees; Onisep, 2018) while there is no prevalence for potential occupational asthma for approx. 40.000 dentists in France derived from the available RNV3P data.

In some use areas the use of engineering controls is limited to general ventilation or absent.

Historically, cast sheet production is the area with the highest exposures, particularly before 1990. At that time 8 h time weighted averages up to 100 ppm and short-term exposures (15 min) up to 2-300 ppm were occurring. No excess of respiratory problems, including respiratory sensitisation, has been reported from this area.

9.4 Exposure-related assessment of cases mentioned in the CLH report

The CLH report for methyl methacrylate proposal document included 71 cases extracted from National Occupational databases (e.g. French RNP3, UK SHIELD/SWORD, Finish FIOH) and additional 8 occupational asthma cases studies were identified from published literature reviews of occupational asthma in allergy and medical journals. A total of 79 cases studies were described in the CLH report and claimed MMA to be the cause of occupational asthma to workers.

To aid case study identification, the cases studies # 44 to 66 from the UK SWORD/ OPRA reports are numbered with the CLH case number first and a second number in brackets (e.g. 45(2)) to reference the information from the SHIELD surveillance 1989-2014 publication (Walters et al. 2017).

The occupational health database information extracted from the CLH document did not provide detailed enough information about the worker activities and their working environment, and often lacked specific composition information about the products handled.

In all these occupational health cases identified, professional workers will have been exposed to a variety of other chemicals and physical respiratory hazards. In over half the cases MMA has been wrongly attributed to be in the products, which could be due to confusion of the chemical wording 'methyl methacrylate' being assumed to be the same as 'acrylate', 'polymethyl methacrylate' and 'cyanoacrylate'.

All the reported CLH document case studies and literature citations were reviewed thoroughly to understand and determine if MMA was specifically used in the products, and if the worker activities cited were likely to make them come into contact with exposure to liquid MMA. The published literature reviews and the SHIELD/SWORD information provided the most detailed information for the assessments. In the remaining occupational health cases, technical knowledge was sought from the respective industry and product literature in order to better understand the likelihood or presence of MMA exposure within the types of products handled by the professional workers. Additional sector specific information was taken from the Chemical Safety Report for methyl methacrylate, and the EU Risk assessment report (2002).

The CLH case studies were collected and assessed into the following groups of information.

- 1 Case studies where MMA exposure is unlikely to be present or irrelevant
- 2 Case studies where MMA exposure is possible but other chemical substances are present resulting in inconclusive causation
- 3 Case studies where exposure to MMA is known
- 4 Case studies where MMA is explicitly advised against

9.4.1 Case studies where MMA exposure is unlikely to be present or irrelevant

The following cases [# 4,7,8,14,15,26,27, 28,29,30,31,32,34,35,42,43,47(4),51(8),54(11),55(12), 56(13),58(15),59(16),61(18),57(14),60(17),62 (19),63(20),67,71] , Publications [65,66,67,73,74,76] have been determined that MMA is very unlikely to be a contributing factor to occupational asthma due to its presence not as liquid MMA or vapour. The activities identified indicate the MMA is mistaken for solid polymer (Poly Methyl Methacrylate) or Cyanoacrylate adhesive (different chemical) and polymerised liquid emulsion paint systems (involving with Acrylate/Methacrylate copolymers). Without specific identifiable formulation data and specific worker activities it cannot be assumed that these professional workers have come into contact with liquid MMA and vapour.

These case studies cover a wide range of industries and worker activities; Automotive, Coatings, Furniture, Plastic manufacturing (including Polystyrene), Inks, light industry, Medical devices, and general medical. Four of the case study sectors in the CLH report were unspecified, and one case study 40# had no information for either its activity and sector. The actual form of the products mentioned in this group are primarily viscous adhesive pastes, liquid emulsion type paints and solid PMMA products.

The reason for misdiagnosis of MMA attributability within this group is primarily due to mistaking the monomer MMA methyl methacrylate for other substances such as acrylates, cyanoacrylates and its polymerizable form Poly Methyl Methacrylate or even other Polyacrylates.

It is known that adhesives and paints can contain residual MMA, (EU risk assessment 2002). In the case of general professional workers using paints in the furniture, metal working, and silkscreen applications they will not come into contact with liquid MMA but PMMA as part of paint formulations .

Many of the adhesive cases cited here, specifically mention cyanoacrylates (UK SHIELD/SWORD case studies) including the teachers exposed to fumes from floor tile adhesives.

The case studies involving the workers in the plastic manufacturing and moulding sector would likely be working with extrusion/moulding facilities using solid PMMA polymer pellets and other fine powder additives, pigments and fillers. It is very unlikely that they would come into contact with liquid MMA but more likely come into contact with polymer dust and extrusion fumes. It also known that polymer beads of very low particulate size distributions can cause respirable irritation if inhaled. Workers in the Polystyrene sector were also mentioned as having asthma from MMA , which would mean other potential chemicals present.

The cases of the midwife using a spray aerosol for medical tissue dressing is likely to have been formulated as solid resin PMMA product with other co-polymers and solvents . The aerosol effect will have contributed to the asthma, but again liquid MMA would not be used for such a direct medical skin contact application due to its skin sensitising properties.

The two cases involving eye lens workers suffering from occupational asthma is likely due their polishing and grinding of solid PMMA (or Poly Carbonate) type resins.

However, it is more likely across all these cited industries and activities that the workers will have come into contact with many other volatile substances (thinners, varnishes, cleaning solvents) and other particulates. These contributing factors are unknown or unspecified within the CLH document.

The total number of cases cited of professional workers claiming to have come into specific contact with MMA (where proven unfounded) is a total of 36 case studies out of the 79 case reported.

9.4.2 Case studies where MMA exposure is possible but other chemical substances are present resulting in inconclusive causation

In following case studies [# 13, 18, 44(1), 46(3), 50(7) 52(9),53(10), 68, 69] , it has been assumed that liquid MMA is the key proponent of the occupational asthma when it can be determined that other chemicals are part of formulations used by specialists for the dental, medical and reactive resin sectors. The prosthetic limb plastic manufacturer [#44(1)] has been included in this group because the formulations used are similar to supplied dental liquid / polymer compositions.

The actual form of the products mentioned in this group are primarily viscous polymer liquids with emulsion type paints and solid PMMA products.

Three specific cases involve dentists, dental assistants and nurses working in dental surgeries. The use of MMA in dental surgeries is not prescribed and dental composite repair work is traditionally carried out using bis GMA and other higher methacrylate monomeric formulations. Additionally, the work conducted by dentists can involve exposure to other particulates due to polishing , grinding, preparation of composite fillers.

The worker handling MMA / PMMA liquid resin systems for the manufacture of prosthetic limbs will have been potentially exposed in a similar way as dental technicians. However, he was also handling glass and carbon fibres, and had worked with Methylene Dissocyanate (MDI) rigid foams, and these were felt to be additional contributing exposure factors.

The remaining cases [#13, 44(1), 46(3),52(9),53(10)] identified in this group involve technicians working on manufactured metal and plastic fabricated products . The data from the SWORD/SHOELD information indicates use of cyanoacrylates in the case of the metal / plastic fabrications and it is known that other metal bonding adhesives such as epoxies are traditionally used as well as 2 component MMA adhesives (which are actually polymerised PMMA) used with initiators. Also, these sectors could have exposed from particulates (metal and polymer) from their polishing/grinding operations.

An electrician Case# 18 working in the construction industry was determined to have received asthma from MMA. No details of the products used were given, (e.g. adhesives, cables, cements) have the health case has been included in this group because of its potential to have come into with many other chemicals, dust and metals used within the construction

Without further occupational health details these asthma occupational health cases cannot be specifically attributed to MMA as many other chemicals , particulates could be or have been present in the workplace environment where these patients worked.

The total number of inconclusive cases of professional workers claiming to have come into specific contact with MMA is determined to be 9 cases studies out of the 79 case reported in the CLH document.

9.4.3 Case studies where MMA exposure is known

Professional workers working within the medical and dental sectors commonly use products formulated with liquid MMA and PMMA resin powders. Many dental and bone cement case studies within the literature have been documented and with the RNVP3 case studies [3,5,6,9,11,16,17,21,22,24,25,33,36,37,41,45 (2),49(6),68], publications [#72, 75,77,78,79] and FIOH case study [70].

It is also known that these dental technicians handle many other chemicals such as PMMA (co-)polymer resin powders, metal powders, initiators, pigments, alginates, gypsum, silicas, and other monomers so that exposure to just MMA is unlikely. Dental technicians' activities also include the polishing and grinding of the final denture/orthodontic articles to provide smooth surfaces and can therefore be exposed to additional polymer type particulates.

One case study # 10 was identified a worker involved with road marking and painting. Although the case did not provide any specific product details it is known that MMA is in road paint formulations, along with other chemicals such as pigments, polymer PMMA powder and initiators .

These skilled trade workers and professional technicians are advised by the manufacturers of products to have adequate safe handling systems in place (LEV, gloves, etc) and specialist training in order to reduce the exposure to all the chemicals and preparations (including MMA) handled.

Therefore, the exposure to MMA is possible but only if the risk management measures are not adequately implemented. The total number of cases of professional workers agreed to be potentially in contact with MMA are 25 cases studies out of the 79 case reported in the CLH document.

9.4.4 Case studies where MMA is explicitly advised against

The case studies [#1,2,12,19,20,23,38,39,48(5)] concerning the nail beauticians and professional workers have been included separately because the use of MMA (and other methacrylates) is strongly advised against for all skin contact applications due to its skin sensitising properties.

Nail products can be used in the polymerized methyl methacrylate, PMMA or other polymer types. It is not uncommon for products to be incorrectly labelled as the monomer instead of polymeric form. Besides methacrylates, other chemicals used in the cosmetic nail sector include acetone cyanoacrylate, formaldehyde, toluene, N-Methyl-2-pyrrolidone, and phthalates. Most of these are well characterized respiratory irritants and could provoke asthma-like symptoms.

In addition, nail and beauty technicians can be exposed to polymeric particulate dust from the nail products when polishing and filing. The number of case studies mentioned of exposure to MMA within the nail care professional workers that are disputed is 9 out of the total 79 case studies.