

Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Methyl methacrylate

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CAS Number: 80-62-6
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Contact details for dossier submitter:

ANSES (on behalf of the French MSCA)

14 rue Pierre Marie Curie

F-94701 Maisons-Alfort Cedex

classification.clp@anses.fr

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1.1 Flammable liquid

1.1.1 BASF, 1968

Study 1 reference:

BASF (1968)

Test type

Method according to DIN 51 755 / Abel Pensky Closed cup

Detailed study summary and results:

Test material: methyl methacrylate, purity not specified

Material and methods: not specified, no GLP

Results

- 10°C at 1013.25

2 HEALTH HAZARDS

2.1 Toxicokinetic

2.1.1 Animal data

2.1.1.1 EU Risk Assessment report, 2002

Study reference:

European Chemicals Bureau. European Union Risk Assessment Report for methyl methacrylate. 2002. 1st Priority list. Volume 22.

Detailed study summary and results:

Test type

Review of the existing data

Test substance

- Methyl methacrylate

Results and discussion

Toxicokinetics: In animals, after oral or i.v. administration of ¹⁴C-labeled methyl methacrylate (oral: 5.7 or 120 mg/kg bw; i.v.: 5.7 or 6.8 mg/kg bw) in rats, 76-88% of the radioactivity is found in expired air within 10 days, 4.7-7.2% in urine, 1.7-3.0% in faeces and the remainder being retained in liver and fat tissues.

Rapid changes of rat blood serum methacrylic acid concentration were observed after administration of a single dose of methyl methacrylate by the stomach tube (approximately 8 mmol/kg bw, equivalent 800 mg/kg bw). The maximum concentration (0.8 mM) was reached between 10 and 15 min after methyl methacrylate administration and decreased over the next 50 min.

After i.v. administration to seven dogs at a total dose of 0.05 ml/kg over a 4-min period pulmonary excretion of methyl methacrylate accounted only for a maximum of 3% of the administered dose. Methyl methacrylate

levels in the expired air were maximal within 2-4 min of the start of the infusion and became negligible after 7 min. After 9 min no methyl methacrylate could be detected in the blood.

Tissue distribution of radioactivity after i.v. administration of labeled methyl methacrylate to three rats was studied by whole body autoradiography. Irrespective of the time of sacrifice the greatest concentrations were determined in blood, heart, lungs, liver, kidneys and salivary glands. Some of the radioactivity was located in the seminal vesicles. It was not possible to determine whether the radioactivity in any of the tissues was due to the presence of methyl methacrylate or its metabolites .

After infusion of the substance (33 mg MMA/kg.min for 3 min) the substance disappeared very rapidly from the blood of the experimental animals (rabbit and dog). The half-life was less than 30 s in rabbit and 41 s in dog.

Metabolism: After oral administration (gavage; 5.7 or 120 mg/kg bw) of radiolabeled methyl methacrylate to Wistar rats, 65% of the dose was exhaled as CO₂ within 2 hr, 76-88% within 10 days. Pulmonary excretion of unchanged methyl methacrylate accounted for less than 1.4% of the dose. Metabolites excreted with urine (4.7-6.0%) were methacrylic acid (0.8% of the dose), methyl malonic acid (1.4%), succinic acid (0.2%), 2 minor metabolites co-eluting with β -hydroxyisobutyric acid and methylmalonic semialdehyde. The authors conclude that methyl methacrylate is metabolised via physiological pathways and enters into the citric acid cycle via methylmalonyl-CoA and succinyl-CoA, which is a part of the valine pathway. After a single i.v. administration to rats of ¹⁴C-labeled methyl methacrylate (5.7 or 6.8 mg/kg bw) the metabolism and excretion of methyl methacrylate were qualitatively the same as after oral administration.

Similar distribution patterns were found after i.p. administration of ¹⁴C-labeled methyl methacrylate to rats. A skin absorption study has been conducted with methyl methacrylate using heat separated human epidermis and a static diffusion cell model. The obtained data indicate that methyl methacrylate can be absorbed through human skin, absorption being enhanced under occluded conditions. Under unoccluded conditions only a small amount of the applied dose (0.56%) penetrated the skin suggesting that evaporation from the surface of the skin is a significant factor when assessing the amount of methyl methacrylate that could be absorbed in any given human exposure scenario.

It has been demonstrated that olfactory epithelium has the highest carboxylesterase activity of all tissues in the upper respiratory tract in rats and humans.

Thus, in conclusion it cannot be accepted to infer a higher NOAEL/LOAEL in man compared to rat because the assumption of the different carboxylesterase activity is confounded by experimental pitfalls and by the anatomical differences between the two species at the site of adverse action which were not appropriately taken into account.

2.1.1.2 Mainwaring et al., 2001

Study reference:

Mainwaring G, Foster JR, Lund V, Green T (2001). Methyl methacrylate toxicity in rat nasal epithelium: Studies of the mechanism of action and comparisons between species. *Toxicology* 158: 109-118

Detailed study summary and results:

Test type

Inhalation exposure of male and female Fisher rats (in vivo and in vitro), Syrian hamsters and humans (in vitro). Non guideline and GLP compliance not specified

Test substance

- Methyl methacrylate (99.9%)

Test animals

- Female F344 rat (150-180g). Groups of 5 rats/dose per experiment
- Male Syrian hamster (100-150g)

Administration/exposure

- *In vitro* metabolism of MMA : Rat or hamster microsomal fractions (liver, 0.008-0.02; olfactory, 0.008-0.012; respiratory, 0.01 mg protein) were incubated in 6 mL sodium phosphate buffer. Reaction was started by the addition of MMA (0.01-1 mM) in DMSO. Human fractions (liver, 0.05; olfactory S9, 0.15-0.17; respiratory S9, 0.24-0.37 mg protein) and rat S9 fractions (olfactory, 0.076; respiratory, 0.057 mg protein) were incubated with 1.0mM MMA.
- Inhibition of carboxylesterase by bis(4-nitrophenyl)phosphate (BNPP) *in vivo* : Four groups of 5 rats dosed IP with BNPP at 0, 50, 75 and 100 mg/kg.
- Effect of carboxylesterase inhibition by BNPP on the development of a nasal lesion in rats exposed to MMA: Groups of rats (n=5) were dosed IP with either saline (10 mg/kg) or 100 mg/kg BNPP in saline (10 ml/kg), 18h, and then again 1h, before being exposed whole body to 200 ppm MMA for 3h or 6h. An equivalent number of control rats were similarly dosed with either saline or BNPP and exposed to air alone. Groups of 5 rats were killed by exposure to haloethane immediately after exposure (1 and 6h) or 18h after the end of a 6h exposure.
- Histochemical localisation of carboxylesterase in nasal tissue sections: Carboxylesterases were localised in rat and human nasal tissues using the methodology described by Bogdanffy et al. (1987).

Results and discussion

- *In vitro* metabolism of MMA : Using either S9 or microsomal fractions, it was shown that the rates of hydrolysis in human olfactory and respiratory tissues were respectively 13 and 7-fold lower than those in the equivalent rat tissues. But this is based on the highest activity seen in human nasal tissues. Comparisons of the metabolic activity in human olfactory and respiratory tissue from the same individual, showed the ratio of activities to be similar to that in the equivalent rat nasal tissues.

- *In vitro* inhibition of carboxylesterase metabolism: The carboxylesterase mediated metabolism of MMA (0.5 mM) to methacrylic acid in rat olfactory microsomes was completely inhibited in both liver and nasal olfactory and respiratory microsomal fractions by BNPP at concentrations of 0.1 mM and above.
- *In vivo* inhibition of carboxylesterase by BNPP: Hepatic carboxylesterase activity, measured with MMA, was almost totally inhibited in S9 sections prepared from tissues taken 4h after a single dose of either 50, 75 and 100 mg/kg BNPP. The enzyme activity in olfactory tissue was reduced to 40 and 10% of control at 50 and 100 mg/kg respectively, whereas respiratory tissue activity was reduced to 66 and 24% of control levels at the same dose levels. The time course showed that both hepatic and nasal activities were maximally inhibited 1 h after dosing and remained significantly reduced up to the end of the experiment at 24 h.
- Effect of carboxylesterase inhibition by BNPP on the development of a nasal lesion in rats exposed to MMA: Based on the results of the experiments with BNPP described above, and the fact that the inhibitor could not be administered to the animals during the exposure period, BNPP was dosed to the animals 18 h, and then again 1 h, before exposure. The nasal passages of rats dosed with either saline or BNPP were morphologically normal at all time points as were the nasal passages of rats exposed to 200 ppm MMA for 3 h, either with or without BNPP treatment. The severity of the nasal lesion seen in rats exposed to MMA for 6 h and killed either immediately after exposure, or 18 h post-exposure, was reduced by prior treatment with BNPP. The lesion was characterised by degeneration/atrophy of the olfactory epithelium and included undulating epithelium, tags of cells streaming from the epithelium, desquamated cells within the airways and areas where only basal cells remained. The lesion was more severe at the 24 h time point, up to 60% of the olfactory epithelium being damaged. Treatment with BNPP before exposure significantly reduced the area of epithelium affected.
- Histochemical localisation of carboxylesterase in nasal tissue sections: In the sections of rat nasal tissue, the enzyme was heavily localised in the tips of the sustentacular cells and in Bowmans glands, a distribution, which is consistent with that reported by Olson *et al.* (1993) using an antibody to the carboxylesterases. In human nasal tissue the enzyme was present in lower amounts in the apical cytoplasm of surface epithelial cells and submucosal glands.

MMA is metabolised *in vivo* by carboxylesterase mediated hydrolysis into methacrylic acid and ultimately carbon dioxide. There is high concentrations of carboxylesterases in rat olfactory epithelium, this metabolic transformation seems to be the origin of the MMA-induced nasal lesion in rats.

In this publication the hypothesis that if MMA induced nasal toxicity is a consequence of its metabolism to methacrylic acid, therefore reducing the activity of the carboxylesterase enzymes *in vivo* should moderate the toxicity of MM has been tested using BNPP, a carboxylesterase inhibitor which was found to specifically inhibit MMA metabolism in the target tissues, both *in vitro* and *in vivo*.

It was demonstrated that the metabolism of MMA in human nasal tissues occurs at significantly lower rates than in the equivalent rat tissue and the relative distribution of the MMA carboxylesterase between olfactory and respiratory tissue was similar in rats and humans. Humans may be less susceptible to the toxic effects of MMA than rats.

2.1.1.3 Morris et al., 1995

Study reference:

Morris JB and Frederick CB. 1995. Upper Respiratory Tract Uptake of Acrylate Ester and Acid Vapors. *Inhalation Toxicology* 7: 557-574.

Detailed study summary and results:

Test type

Basic *in vivo* toxicokinetics study not performed according to a guideline or GLP compliant.

Test substance

- Methyl methacrylate (no additional information)

Test animals

- 45-70 day-old male rat Fisher 344 (Charles River) weight: 160-230 g
- 3-5 males per group exposed to (measured): 0, 0.090, 0.437 and 2.262 mg MMA/L (corresponding to 0, 25, 100 and 500 ppm)

Administration/exposure

The upper respiratory tract (URT) of rats was used as a model to determine the uptake of MMA and provide preliminary biochemical response data.

The animals were exposed in a nose-only inhalation chamber via the tube for 60 minutes to air or MMA at concentrations of 90, 437 or 2262 mg/m³. Uptake of MMA by the URT was determined by constant velocity unidirectional flow and cyclic flow conditions (the latter considered to represent a closer surrogate for normal breathing patterns while the former provided for precise measurements of dosimetry). The animals were either not treated or pretreated with bis-nitrophenylphosphate (BNPP, a carboxylesterase inhibitor) to determine the influence of metabolic ester hydrolysis by the nasal carboxylesterases. Deposition efficiency was determined by the difference in the MMA concentration entering and leaving the chamber.

Results and discussion

Regarding the toxicokinetics the data suggest that MMA deposits with 10-20% efficiency in normally breathing rats. About the metabolite characterisation, BNPP significantly reduced MMA deposition on URT (by one-third) confirming that MMA is metabolized in nasal tissue by carboxylesterase. MMA exposure decreased nasal nonprotein (NPSH) content by approximately 25% ($p < 0.05$) at their respective high exposure concentrations, but not at the lower exposure concentrations. Methacrylic acid deposition efficiencies averaged 95 % or greater under unidirectional flow. Nasal NPSH level was not decreased by

exposure ($p > 0.05$) even at delivered dose rates twofold or more greater than for the ester, suggesting the nasal NPSH lowering effect is attributable to the ester vapor itself, not its acid metabolite.

2.1.1.4 Paulet et al., 1979

Study reference:

Paulet G, Desbrousses S, Toulouse P (1979). Toxicologie du methacrylate de methyle. Evolution de sa concentration dans le sang chez le lapin et le chien in vivo. Arch. Mal. Prof. Med. Trav. Sec. Soc. 40, 604-611.

Detailed study summary and results:

Test type

Study to determine half-life of MMA. Not GLP compliant. Does not follow a guideline.

Test substance

- Methyl methacrylate

Test animals

- Rabbits and dogs

Administration/exposure

- Infusion of MMA of 33 mg/kg.min for 3 min

Results and discussion

MMA disappeared very rapidly from the blood of the experimental animals. Half-life was less than 30s in rabbits and 41s in dogs.

2.1.1.5 Raje et al., 1985

Study reference:

Raje RR, Ahmad S, Weisbroth SH. Methylmethacrylate: tissue distribution and pulmonary damage in rats following acute inhalation. Research Communications in Chemical Pathology and Pharmacology. October 1985, 50(1):151-154.

Detailed study summary and results:

Test type

Study to test the local and systemic effects after an exposure to MMA via inhalation route. Not GLP compliant. Does not follow a guideline.

Test substance

- Methyl methacrylate

Test animals

- Rats

Administration/exposure

- Inhalation route
- Exposure to 100 ppm of MMA for 1, 2, 3 or 4 hours.

Results and discussion

After inhalatory exposure with 100 ppm methyl methacrylate to rats for 1, 2, 3, and 4 hours, concentrations of methyl methacrylate were found to be about 11 mg/100 ml in blood, about 21 µg/g in lungs and about 25 µg/g in brain (independent of the exposure time) at the end of exposure.

Local and systemic effects of single inhalation exposures of rats to methyl methacrylate were reported in two other studies. Inter-alveolar congestion/haemorrhage, pulmonary vasodilatation and oedema were observed with rats exposed to 100 ppm (~0.410 mg/l) for 2, 3 and 4 hours, but not for 1 hour. No histopathologic changes were seen in the brain of any of the exposed rats.

Authors tested the local and systemic effects following inhalation of 100 ppm (circa 0.410 mg/L) of methyl methacrylate by rats using different exposure periods. The changes observed were inter-alveolar congestion/haemorrhage, pulmonary vasodilatation and oedema, observed after an exposure time of 2 hours or 4 hours, but not after an exposure of 1 hour. The authors conclude that this indicates that MMA has a direct irritant action on pulmonary capillaries as well as on alveolar capillaries. This interpretation of the findings seems plausible.

2.1.2 Human data

2.1.2.1 European Union risk Assessment report, 2002.

Study reference:

European Chemicals Bureau. European Union Risk Assessment Report for methyl methacrylate. 2002. 1st Priority list. Volume 22.

Detailed study summary and results:

Test type

Toxicokinetics: Five min after the insertion of the bone cement into the femoral cavity both methyl methacrylate and its metabolite methacrylic acid (MAA) were detected in significant quantities, concentrations of MAA tending to lag behind those of methyl methacrylate. The authors therefore conclude that the initial step of methyl methacrylate metabolism in vivo is hydrolysis to MAA catalysed by nonspecific serum esterases.

The amount of exhaled methyl methacrylate was dependent on the surgical technique.

Arterial blood levels were lower than venous blood levels. Maximum venous methyl methacrylate blood levels in nine patients 2 to 10 min after tourniquet release during knee arthroplasty ranged between 0.1 and 1.44 µg/ml. The half-life of methyl methacrylate in blood was reported to be 47 – 55 min.

Concentrations of methyl methacrylate in blood of patients with a hip arthroplasty, receiving about 48 g of a half-cured methacrylate bone cement, varied widely. Maximum blood levels were obtained between 30 and 60 s after implantation with mean concentration of 0.8 – 1.2 µg/ml. In samples taken after 3 and 6 min, methyl methacrylate could not be detected. From these data, an initial half-life of 0.3 min and a terminal half-life of 3 min were calculated which is in contrast to the data reported earlier.

Toxicokinetics seem to be similar in man and experimental animal. After arthroplasty using methyl methacrylate-based cements, exhalation of unchanged ester occurs to a greater extent than after i.v., i.p. or oral administration. After oral or parenteral administration methyl methacrylate is further metabolised by physiological pathways with the majority of the administered dose being exhaled as CO₂. Conjugation with GSH or NPSH plays a minor role in methyl methacrylate metabolism and only occurs at high tissue concentrations.

2.2 Respiratory sensitisation

2.2.1 Animal data

No data

2.2.2 Human data

2.2.2.1 French national network for the monitoring and prevention of occupational diseases (RNV3P) database (2001-2017)

Study reference:

43 cases found in the RNV3P database

Detailed study summary and results:

Test type

The French RNV3P network is composed of the 30 Occupational disease consultation centres (CCPP) in mainland France and a number of occupational health services (SSTs) associated with the network. This network's goal is to record the data from consultations in a national database (patient demographics data, diseases, exposures, job sectors and professions). After investigation, the expert physicians from the CCPPs establish a possible link between the occupational exposure(s) and the pathology which motivated the consultation (this causal link is recorded in the data base) with a level of attributability (low, moderate or high). The level of imputability which links an occupational exposure and a disease is the analysis to determine if, for a specific patient, the substance to which he/she is exposed to during work is responsible for the detected pathology. In the RNV3P database 4 levels of attributability exist:

- 0 = No causal link
- 1 = Low: low or questionable link
- 2 = Moderate: Possible link or direct but not essential
- 3 = High: High, direct and essential link

Cases found in the RNV3P following a search for:

- Asthma/Allergic asthma in workers following an occupational exposure to methyl methacrylate reported by the occupational physician from CCPP (Occupational disease consultation centres) with a high or moderate level of attributability.

2.2.2.2 Surveillance of Work-Related and Occupational Respiratory Disease (SWORD) database from UK (between 1989 and 2017)

Study reference:

23 cases found in the SWORD database

Detailed study summary and results:

Test type

There have been 23 actual (78 estimated) cases of occupational asthma attributed to methyl methacrylate reported to the UK Health and Occupation Research Network (THOR) by the chest physicians to the Surveillance of Work-Related and Occupational Respiratory Disease (SWORD) between 1989 and 2017. It has to be noted that:

- 61% of the cases were reported in males;
- Mean age (all cases) 43 years (age range 18-77 years);
- The industry sectors reported for the cases were as follows: 11/23 (48%) Health and social care; 8/23 (35%) manufacturing; and 1 case reported in each of the following industries, education, construction, other service activities, other business activities.

There is no information on the attributability of the case.

2.2.2.3 Occupational Physicians Reporting Activity (OPRA) from UK (between 1996 and 2017)

Study reference:

1 case

Detailed study summary and results:

Test type

In addition to the previous cases reported to the UK Health and Occupation Research Network (THOR) one other case of occupational asthma attributed to methyl methacrylate was reported to THOR by occupational physicians in the Occupational Physicians Reporting Activity (OPRA) between 1996 and 2017. The case was reported in a male working in the manufacture of medical devices.

There is no information on the attributability of the case.

2.2.2.4 Finnish Institute of Occupational Health (FIOH) from Finland (between 1997 and 2018)

Study reference:

4 cases from the FIOH database

Detailed study summary and results:

Test type

A relatively large proportion of suspected occupational asthma cases due to chemicals is investigated at the Finnish Institute of Occupational Health (FIOH), where also specific inhalation challenges (SIC) with workplace agents are performed. The cases are referred to FIOH for confirmation of the diagnosis from all over Finland. During 1997-2018, four cases of occupational asthma to MMA were diagnosed at FIOH. Of these, one case had an early reaction (asthma reaction within 1 hour after exposure), two cases had late (meaning after 1-8 hour after exposure) SIC and one with both early and late reaction

2.2.2.5 Marez et al., 1993

Study reference:

Marez T, Edme JL, Boulenguez C, Shirali P and Haguenoer JM. Bronchial symptoms and respiratory function in workers exposed to methyl methacrylate. 1993. Brit. J. Ind. Med. 50, 894-898.

Detailed study summary and results:

Test type

The authors investigated the lung function parameters in eight workers with more than five and less than 10-year exposure and 32 workers with more than 10-year exposure to methyl methacrylate in two factories with mean concentrations of 18.5 and 21.6 ppm (ranges of 9-32 ppm and 11.9-38.5 ppm). 13 of the 40 workers were non-smokers, 11 were ex-smokers and 16 were smokers. An increased incidence of chronic cough was observed in 8 out of 40 exposed workers and 2 out of 45 controls with similar smoking habits. Spirometric values did not differ before the workshift, but decreased in controls and exposed workers during the workshift. The decrease of two parameters out of nine, the maximum expiratory flow (MEF) when 50% of the forced vital capacity remained to be exhaled and the ratio of MEF to maximal expiratory flow, were significantly higher in the exposed workers. There was no interaction of smoking habit and methyl methacrylate exposure related to the functional parameters. The increased cough incidence and the mild airway obstruction were correlated to the methyl methacrylate exposure. 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 longtime 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 workshift. 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.

2.2.2.6 Pickering et al., 1986

Study reference:

Pickering CAC, Brainbridge D, Birtwistle IH, Griffiths DL. Occupational asthma due to methyl methacrylate in an orthopaedic theatre sister. 1986. Brit. Med. J. 292, 1362-1363

Detailed study summary and results:

Test type

There is a report of a 56-year-old theatre sister, who smoked 10-20 cigarettes daily, had worked in an orthopaedic operating theatre for 11 years. During this period she had regularly handled bone cement, over the last seven years making about 12 mixes weekly. Before presentation she had handled a new cement mixed by the use of liquid methyl methacrylate, and developed respiratory symptoms characterized by a persistent cough with wheezing and breathlessness. The association between her symptoms and work became apparent. A challenge test with MMA resulted in late asthmatic reactions. The asthmatic symptoms were due to exposure of transient and high levels of MMA vapour. Pulmonary function tests, when she was not working, yielded normal results.

2.2.2.7 Röhm GmbH, 1994

Study reference:

Röhm GmbH. Medical examination of workers in acrylic sheet production exposed to methyl methacrylate. Personal communication. 1994

Detailed study summary and results:

Test type

In an acrylic sheet production plant 211 male workers exposed to methyl methacrylate were examined in a medical survey consisting of a self-questionnaire about lifestyle, occupation and medical history with emphasis on complaints of nose, throat and respiratory system failures, and allergic reactions including skin and asthmatic reactions. The questionnaire was supplemented by a detailed anamnesis and anterior rhinoscopy using a speculum. The workers (mean age 37 years) spent an average of 8.8 years (<1 until >20 years) in acrylic sheet production. 55 subjects starting to work in the factory during the report period without any prior exposure to methyl methacrylate were examined in the same manner. Present exposures to methyl methacrylate varied between <3 and 40 ppm (<12 and 160 mg/m³) (8-hour average value). Past exposures were between 10 and 70 ppm (4 and 290 mg/m³) methyl methacrylate. Occasional short-term peak concentrations of 100 – 680 ppm (410 and 2,800 mg/m³) had also been recorded. No case of methyl methacrylate exposure related respiratory or skin sensitisation was observed in the exposed groups. Observation of irritation in the eyes and the upper respiratory tract was reported to be limited to acute and reversible reactions after short-term peak exposures at concentration levels exceeding 100 ppm (410 mg/m³) (without any proof for the correlation). There were no indications for clinical symptoms of a work-related rhinopathy or any substance related abnormalities in the nasal cavity in the exposed group. The study did not include data on the exposure to other chemicals; there was no control group, no statistical evaluation was performed.

2.2.2.8 Roth et al., 2017

Study reference:

Roth E., Kristiansen C.B., Assing K.D. and Weinreich U.M.. Work-related asthma in an orthopaedic surgeon. 2017. Ugeskr Laeger. 2017 Jul 24;179(30).

Detailed study summary and results:

Test type

An orthopaedic surgeon with no history of lung disease developed cough and dyspnoea. The patient was diagnosed with asthma by spirometry and bronchial provocation test with methacholine. A clear correlation between symptoms and work was established meriting a referral to a centre for occupational health. The patient was diagnosed with work-related disease, which was recognized by the industrial injury board. The cause was methyl methacrylate, a known airway irritant, which is an important component of bone cement. Previously, no cases of work-related asthma in orthopaedic surgeons have been reported.

2.2.2.9 Savonius et al., 1993

Study reference:

Savonius B, Heskinen H, Tuppurainen M, Kanerva L. Occupational respiratory disease caused by acrylates. 1993a Clin. Experim. Allergy 23, 416-424.

Savonius B, Heskinen H, Tuppurainen M, Kanerva L. Erratum: Occupational respiratory disease caused by acrylates. 1993b. Clin. Experim. Allergy 23, 712.

Detailed study summary and results:

Test type

In a first publication, authors reported 3 cases of respiratory sensitisation that they have linked with exposure to MMA. The nomenclature used in the original publication was confusing and indicated that the individuals in question were exposed to methyl cyanoacrylates rather than to MMA. The authors have, however, published an erratum in which they specify that 3 of the individuals were exposed to MMA. Patient M1, a 48 year old female, is alleged to have been exposed to MMA during the use of a glue (composition unspecified) during plate engraving and is reported to have developed respiratory distress at work, strain, sneezing, rhinorrhoea and stuffiness. Challenge to the implicated glue caused a maximal 24% fall in PEF values and her symptoms persisted on transfer to the use of a cyanoacrylate glue. Patient M2, a 32-year-old male involved in the assembly of hearing devices, showed a small maximal 15% decrease in PEF values following the grinding of “a piece of methacrylate” in an exposure chamber. The third patient, M3, was a 46-year-old female who had worked for about 20 years as a dental technician. She developed paraesthesia on the unlar side of both hands but not dermatitis. She subsequently experienced a feeling of tickling in her throat, yawning, cough, tiredness and chest tightness; the symptoms subsided on sick leave and vacations but recurred within a week at work. Simulated occupational exposed to “methacrylate powder and methacrylate liquid” for 30 minutes resulted in a maximal fall of 26% in PEF value. Skin prick test to “methacrylate” was

negative. Although this case report appears to show an association between occupational exposure to “methacrylate liquid” and the respiratory symptoms observed it is not possible from the data provided to conclude that the symptoms resulted from exposure to MMA. Therefore consideration of the available data from the 3 cases reported by the authors do not show sufficient evidence of respiratory sensitisation by MMA.

2.2.2.10 Scherpereel et al., 2004

Study reference:

Scherpereel A., Tillie-Leblond I., Pommier de Santi P. and Tonnel A.B. Exposure to methyl methacrylate and hypersensitivity pneumonitis in dental technicians. 2004. *Allergy* 59 (8): 890-892.

Detailed study summary and results:

Test type

Study reports 2 cases of dental technicians with a diagnosis of hypersensitivity pneumonitis due to an inhalation exposure to MMA:

- 24-year old female with an exposure during 6 months as dental technician that led to severe dyspnoea and hypoxemia. She had to quit her job.
- 20-year old female hospitalised for acute respiratory distress. She had also hypoxemia. Effects were due to an occupational exposure as dental technician student.

2.2.2.11 Uriarte et al., 2013

Study reference:

Uriarte SA, Fernández-Nieto M, Sastre J. (2013). Occupational asthma due to polyvinyl chloride and methyl methacrylate in a plumber. *Investig Allergol Clin Immunol.* 23(6):437-8.

Detailed study summary and results:

Test type

This study reported a case of a 48-year-old man with no history of atopy who worked as a professional plumber for over 30 years and had consulted for progressive dyspnea and dry cough during the last 3 years. His symptoms were triggered at work and persisted outside work. The patient had never had skin lesions and never used protective clothing, gloves, or a mask at work. He has been on sick leave for 24 months with persistent symptoms and no treatment. After performing a SIC for MMA the asthma reaction following an exposure to the substance was confirmed.