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Subject: Finalising the methyl methacrylate CLH dossier

Dear Tim Bowner

Thank you for your request (D(2021)0116) regarding the report of Suojalehto et al. 2019 and specific inhalation challenges (SIC) to methyl methacrylate (MMA).

In the series of 55 occupational asthma cases caused by acrylates (Suojalehto et al. 2019), we identified six cases caused by MMA with high certainty. Three of these cases (#68-70 FIOH database) are also mentioned in ANSES CHL report (EC Number 201-297-1).

Please find our responses to your specific queries below.

1. The MMA exposure levels used in the SICs included in Suojalehto et al. 2019, or information otherwise relevant to them (for instance if and how it was determined that the exposure levels were below irritating concentrations, if exact concentrations were or were not measured).

Of the six MMA cases in the Suojalehto et al. 2019 report, three (2 dentists and 1 dental technician) were diagnosed in the Finnish Institute of Occupational Health (FIOH) from where we have detailed information on the exposure levels in SICs. FIOH has used a stable SIC protocol for two-component (monomer liquid + polymer powder) MMA-based methacrylate products since 2000. These are used typically in dental and other prosthetic work as well as in preparing nails by the "acryl technique". In the three cases the products' main component (>90% in liquid component) was MMA according to the SDS or ingredient list.

The FIOH protocol includes mixing 4-5 ml of MMA monomer liquid with a suitable amount (according to the product specification) of methacrylic polymer powder. MMA level was not measured in the three specific cases reported in Suojalehto et al. 2019. However, we have measured MMA in exactly similar SICs, using the same chamber and having similar conditions such as humidity, temperature and ventilation. Data of five measurements during 2007-2020 are available; the concentrations were 0.56, 3.6, 5.1, 5.6 and 13 mg/m³ (median 5.1). These correspond to 1-31 % of the Finnish 8-hour occupational exposure limit (OEL), 42 mg/m³. The highest value is an outlier which might be due to contamination in the sensitive analysis. It is extremely unlikely that any of the three FIOH MMA cases were exposed to more than this level during the SIC.

Due to similar products and SIC protocols, it is likely that the exposure levels in two MMA cases diagnosed in other units were comparable to those of FIOH. In the third case the patient ground a recently hardened prosthesis during SIC. Air measurements in similar SICs in the FIOH have produced about 1/10 of the MMA concentration measured during mixing of liquid and powder.

2. The number of cases where specifically MMA could be determined as the likely causative agent for respiratory sensitisation in the cohort as opposed to other acrylates, and how this was determined.

In the series by Suojalehto et al. 2019, six patients had been both predominantly exposed to MMA and also tested positive specifically for this substance in the SIC. This was judged based on the information on workplace agent that was also used in the respective SIC. During the study period, two-component, self-curing methacrylate products used in e.g. dental and other prosthetic work as well as in preparing nails by the “acryl technique”, have typically contained MMA as their main ingredient. In the FIOH cases we were able to verify from the original product information that this was indeed the case. The three cases from other centres comprised : (a) a beautician reported by the Department of Allergy, Fundacion Jimenez Diaz and CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain, (b) a dental technician reported by the Department of Chest Medicine, Centre Hospitalier Universitaire UCL Namur, Yvoir, Belgium and (c) a prosthesis technician reported by the Department of Chest Diseases, University Hospital of Strasbourg, Strasbourg, France. Based on the product information provided by the respective centres we concluded that they had used two-component MMA products to make prostheses. In these cases the respective SIC had been performed by (a) mixing liquid + powder similarly to the FIOH protocol , (b) by handling of 5 ml of monomeric liquid part of a two-component prosthesis product (the same product had been used also in the FIOH) or (c) by sanding an audio-prosthesis previously made from liquid and powder.

3. The type of reaction these cases had in the SIC.

Three of the MMA challenge-positive patients had a delayed reaction to the MMA challenge, two had a bi-phasic reaction (meaning both early and delayed), and one had an isolated early reaction. Five of six cases experienced delayed (or bi-phasic) response that is considered a hallmark of an immunological response.

4. The occupations of these cases.

Two were dentists, three were dental/prosthetic technicians, one was a beautician.

5. Any relevant information on irritative responses to MMA in asthmatics (for example data on asthmatics that did not react to MMA in SIC).

In Suojalehto et al. 2019 we did not report data on negative SICs. In the FIOH during 2013-2019 seven patients were tested due to occupational asthma suspicion to MMA with negative SIC results, five of them had asthma diagnosis. Altogether 16 challenges (12 challenges to patients with asthma diagnosis) with negative results with products containing only or predominantly MMA were performed. In 11/16 of these challenges, the tested product contained >90-95% MMA, or MMA and non-sensitising solvents. In 3/16 challenges, the exposure was to a mixture of 50-100% MMA and ≤ 10% TMDMA. In 1/16 challenges, a mixture of 50-70% MMA and < 0% triethyleneglycol dimethacrylate was used, and in 1/16 challenges a mixture of 50-70% MMA and other methacrylates was used. In all of these cases, the SIC aimed to recreate an exposure comparable to that at the patient’s workplace.

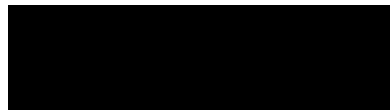
6. Overlapping of cases in Suojalehto et al. 2019 and Walters et al. 2017; this is particularly important for us to understand the numbers of unique cases.

There are no overlapping cases in the Suojalehto et al. 2019 and Walters et al. 2017 publications.

SIC is the reference standard for the diagnosis of occupational asthma. Our report (Suojalehto et al. 2019) is of 55 cases identified using this technique independently in different centres across Europe over a specified time period; most centres have made further diagnoses before and after this period. The patients in the series we reported had a wide variety of occupations which shared only workplace exposures to acrylates, including in some cases MMA. Collectively, we believe this experience provides strong evidence that certain acrylates, including MMA, have the potential to sensitise the respiratory tract and induce occupational asthma.

With best wishes

On behalf of the European Network for the Phenotyping of Occupational Asthma (E-PHOCAS) investigators



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