Epidemiology studies of populations with occupational exposure to MMA

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In order to find epidemiology studies on MMA exposed populations PubMed was searched on several occasions. Searches were conducted on July 10 2018, with combinations of key terms "Methyl Methacrylate" AND "Epidemiology" and "Methyl Methacrylate" AND "Exposure". The searches were restricted to studies on humans. The literature searches yielded publications on 6 epidemiology studies of populations occupationally exposed to MMA.

MMA production

On various occasions epidemiology studies have been conducted on worker cohorts that had been involved in MMA-monomer or MMA-polymer production to evaluate their long term health status and potential impact of their occupational exposures. Studies on MMA cohorts have been conducted in the United States[1, 2], Great Britain [3] and Russia [4]. In the United States, Walker et al published the results of a cohort mortality study on 13,863 workers from two MMA-monomer production and MMA-polymer sheet production facilities with first exposure occurring in 1932.[2] The cohort was restricted to 9,072 workers after certain eligibility criteria were applied. The cohort was followed for cause specific mortality until 31 December 1986. All-cause mortality and mortality from malignant neoplasms were lower than expected. In the Bristol cohort, the sub-cohort of workers that had been employed prior to January 1 1946 an excess of colon cancer mortality was reported in the men with the highest cumulative exposure (SMR =2.4 95% CI: 1.33-4.34).

The second study conducted in the United States followed a cohort of 1,561 men involved in MMA-monomer production at two locations, between 1951 (year of start-up) and 1974 for cause specific mortality, until 31 December 1983.[1] Follow-up was complete for 98% of the cohort and smoking data were available for the majority of the study population. Before the end-date of follow-up 114 workers from the exposed sub cohort had died compared to an expected number of 169.7 based on the general population mortality rates. All cancer mortality and specific subsite cancer mortality were in the range of what was expected. The authors reported no excess cancer mortality from any type.
In Great Britain workers of two MMA-polymer sheet production sites, employed between 31 December 1948 and 31 December 1988 were followed for cause specific mortality until 31 December 1995. The exposed cohort consisted of 4324 workers involved in MMA-polymer sheet manufacturing. Vital status follow-up was remarkably complete at 98%. Exposure assessment demonstrated that at some workplaces exposure to MMA was up to 100 parts per million. At the end of follow-up, 1322 workers had died which was lower than the expected number based on the general mortality rates. In all, no indication for an increased cancer risk from MMA was noted.

A fourth retrospective cohort mortality study on workers in MMA and MMA sheet production was conducted in Russia.[4] The MMA sub cohort consisted of 3914 workers employed for at least three years and between 1938 and 1945. Completeness of vital status was 89.8%. All cause and all cancer mortality was close to expected, but a non-significant increase in intestinal cancer was noted (SMR=1.38, 95% CI: 0.38-3.53).

These studies were all extensively reviewed by Tomenson et al.[5] The authors concluded that the results of the reviewed studies did not suggest that MMA exposure was responsible for the excesses of

respiratory and stomach cancer and that these were more likely caused by unexplained contributions of lifestyle such as cigarette smoking and diet. They also concluded that the lack of consistency across studies and the absence of a dose response indicated that MMA exposure had not resulted in any cancer excess in these cohorts, and concluded that the studies provide no convincing evidence for a carcinogenic risk associated with MMA exposure.

MMA in surgery

After the publication of the extensive review by Tomenson *et. al*. a study was reported on cancer mortality among orthopedic surgeons in the United States.[6] Orthopedic surgeons may come into contact with MMA because it is a component of bone replacement materials during polymerization. A proportionate cancer mortality analysis was conducted to compare cancer mortality in 468 male orthopedic surgeons with that of 1890 general surgeons who died between 1991 and 2001. The authors provide no evidence in their publication as to whether or at what levels the orthopedic surgeons were exposed to MMA. Cause of death information on these 2358 surgeons was obtained from the national death index system. The authors noted that the orthopedic surgeons were dying from cancer at an earlier age than the general surgeons and reported an elevated risk of cancer of the esophagus and myeloproliferative cancers.

No exposure data or information on confounding factors was available. However, and more importantly, proportionate mortality analyses have several structural weaknesses. First, the lack of information on the underlying population and thus proper incidence or mortality rates cannot be compared. Proportionate Mortality Ratio (PMR) studies are thus generally regarded as inferior to the classic retrospective cohort studies. They are seen as the last resort in situations where data on the entire cohort are lacking and when it is impossible to retrospectively enumerate the cohort.[7, 8] Second, PMR studies are also susceptible to selection bias because of the intrinsic lack of information on the entire cohort. Morevover, Diaz et al incorrectly applied the PMR methodology. In a PMR analysis age specific proportions of mortality from a certain disease are applied to a certain standard population. By applying this method the expected number of deaths from a certain disease in that age group can be calculated. The sum of these expected numbers gives the total number of expected deaths from that disease in the total number of observed deaths. The ratio of the observed number over the expected number of deaths is the PMR, which as an estimate of the relative risk. The analysis carried out by Diaz et al did not result in a PMR adjusted for the effect of differences between the age distributions and therefore the effect of age differences remained uncontrolled. In other words, the results presented by Diaz can simply be a result of a difference in age distribution between the orthopedic surgeons and the general surgeons who died between 1991 and 2001. There are substantial differences in age distribution between the American colleges of orthopedic surgeons and the college of general surgeons. This is indicated by table 2 of the article, depicting an average age at death of 70 for the orthopedic surgeons as compared to 79.2 for the general surgeons. The orthopedic surgeons are a younger population than the general surgeons . Causes of death vary between age groups. For example death rates from motor vehicle accidents are typically higher in younger age groups and cancer mortality rates are higher in older age groups. The effect of these differences leads to a higher percentage of deaths from motor vehicle accidents in younger populations as compared to older populations. It is therefore critical to take the age distributions into account when comparing proportional mortality rates between groups. Diaz did not properly adjusted for the impact of different age distributions between the orthopedic surgeons and general surgeons.

Furthermore, the initial sample size of the study was 3458 deaths. Since for 885 deaths insufficient data were available for obtaining the cause of death the populations was limited to 2358, a loss of 25% of the original population. It is questionable if the remaining 2358 deaths are representative for the 3458 originally identified deaths.

In 2012 Chou et al published the results of a second study, now among female orthopedic surgeons.[9] The survey contained questions about cancer prevalence and exposure to MMA-based bone cement, ionizing radiation and risk factors for breast cancer. The response rate was 69.7%. A higher self-reported breast cancer prevalence was noted in the female orthopedic surgeons as expected based on a national prevalence data. The authors compared the reported prevalence of well-established breast cancer risk factors in the female orthopedic surgeons with those collected in a general health survey and noted that some risk factors were lower and others were higher. Particularly nulliparity and older age at first pregnancy, strong risk factors for breast cancer, were more prevalent in the orthopedic surgeons than in the general population. However the authors could not adjust for the effect of these factors. The self-reported prevalence of frequent exposure to PMMA, as in MMA-based bone cement, in the cancer cases did not differ of that reported by the non-cases. In a second similar study Chou attributed the reported elevated breast cancer prevalence to exposure to ionizing radiation in the form of fluoroscopy and did not mention PMMA as a possible risk factor.[10] Elevated breast cancer rates have been reported in physicians with no exposure to MMA as well.[11]
In Table 1 the key characteristics of the 6 epidemiology studies on MMA are further specified (see Table 1).

Conclusion
In summary, a total of 6 epidemiology studies have been conducted on occupational populations with exposure to MMA; four in the MMA-monomer production and/or MMA-polymer sheet production industry and two among orthopedic surgeons. No consistent elevations of specific cancer types were reported. In some studies increased cancer rates were reported, but these findings are most likely attributable to faulty methodology (orthopedic surgeon studies). The conclusion drawn by Tomenson et al in 2005 following a review of the then available epidemiologic literature, that the available human data are not in support of an increased cancer risk from occupational exposure to MMA remains correct. In particular the retrospective cohort studies conducted in the United States, and Great Britain had a significant sample size of a combined number of over 15,000 employees, with nearly complete follow-up and latency periods of potentially reaching over 60 years. These studies evaluated exposure concentrations as high as the 100 ppm range, far in excess of exposures present in industry over the last few decades. These cohorts present the most comprehensive information available on the occurrence of cancer in humans exposed to high concentrations of MMA. Cancer mortality rates in these large cohorts, followed over extensive time periods and with the high MMA concentrations experienced in the early production decades, with longest follow-up, are similar to those in the general population. These results demonstrate that exposure to MMA, even at relatively high concentrations, is not associated with cancer risk.

References

[1] Collins JJ, Page LC, Caporossi JC, Utidjian HM, Saipher JN: Mortality patterns among men exposed to methyl methacrylate. J Occup Med 1989, 31:41-6.
[2] Walker AM, Cohen AJ, Loughlin JE, Rothman KJ, DeFonso LR: Mortality from cancer of the colon or rectum among workers exposed to ethyl acrylate and methyl methacrylate. Scand J Work Environ Health 1991, 17:7-19.

[3] Tomenson JA, Bonner SM, Edwards JC, Pemberton MA, Cummings TF, Paddle GM: Study of two cohorts of workers exposed to methyl methacrylate in acrylic sheet production. Occup Environ Med 2000, 57:810-7.
[4] Geiko OI, Fedotova IV, Blagodatin VM: [Epidemiologic-hygienic aspects of the assessment of carcinogenic risk in methacrylate production]. Med Tr Prom Ekol 1996:4-7.
[5] Tomenson JA, Carpenter AV, Pemberton MA: Critical review of the epidemiology literature on the potential cancer risks of methyl methacrylate. Int Arch Occup Environ Health 2005, 78:603-12.
[6] Diaz JH: Proportionate cancer mortality in methyl methacrylate-exposed orthopedic surgeons compared to general surgeons. J Med Toxicol 2011, 7:125-32.
[7] S H: "Occupational Epidemiology", in Exposure Assessment for Epidemiology and Hazard Control, ed. S. M. Rappaport and T. J. Smith, Lewis Publishers, Chelsea, MI, 1991.
[8] Checkoway H, Pearce N, Kriebel D., Research Methods in Occupational Epidemiology: Oxford University Press, 2004.
[9] Chou LB, Chandran S, Harris AH, Tung J, Butler LM: Increased breast cancer prevalence among female orthopedic surgeons. J Womens Health (Larchmt) 2012, 21:683-9.
[10] Chou LB, Lerner LB, Harris AH, Brandon AJ, Girod S, Butler LM: Cancer Prevalence among a Cross-sectional Survey of Female Orthopedic, Urology, and Plastic Surgeons in the United States. Womens Health Issues 2015, 25:476-81.
[11] Lee YS, Hsu CC, Weng SF, Lin HJ, Wang JJ, Su SB, Huang CC, Guo HR: Cancer Incidence in Physicians: A Taiwan National Population-based Cohort Study. Medicine (Baltimore) 2015, 94:e2079.

Table 1: Overview of the published epidemiology studies on MMA cohorts

First Author	Study population	Sample size	Study design	Strengths	Weaknesses	Results
Walker	MMA production and sheet production (USA)	9,072	Retrospective cohort mortality study	Longitudinal design. Exposure measurement data available. Long period of exposure and follow-up	Cancer mortality only. No adjustment for confounders	Excess of colon cancer in the highest exposed sub cohort
Collins	MMA production (USA)	1,561	Retrospective cohort mortality study	Longitudinal design. Exposure measurement data available, 98% complete follow-up, smoking data taken into account	Cancer mortality only. No adjustment for confounders	Cancer mortality by sub types as expected based on general population rates. Absence of dose response relationship
Tomenson	MMA production and MMA sheet production (GB)	4,324	Retrospective cohort mortality study	Longitudinal design. Exposure measurement data available	Cancer mortality only, no adjustment for confounders	No cancer risk from MMA exposure reported
Geiko	MMA production (former Soviet Union)	3,914	Retrospective cohort mortality study	Longitudinal design.	Lack of exposure data, cancer mortality only, no adjustment for confounders	Non-statistically significant excess of intestinal cancer
Diaz	Orthopedic surgeons	468	Proportionate mortality study		No cause of death for 25% of the original population, inferior research design, faulty statistical analysis with no adjustment for age, no exposure information	Increase in esophagus cancer and myeloproliferative malignancies
Chou	Female orthopedic surgeons	505	Postal survey	Data on confounding factors collected, but not taken into account	Lack of exposure data, self-report data on cancer, lack of longitudinal component, cross-sectional design	Increased risk of breast cancer