Results of the Hardmetal Epidemiology Study – an International Investigation

The following article is an overview of the background and results of the study by Dr Gary Marsh, Professor of Biostatistics, Epidemiology and Clinical & Translation Health Science, and Director of the Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. Dr Marsh served as the principal investigator of the international study of hardmetal workers that was sponsored by three member companies of International Tungsten Industry Association (ITIA), with one non-member company and the Cobalt Institute (formerly Cobalt Development Institute) adding their support. The study began in 2011 and was completed in 2017. Final results of the study were presented by the various country-specific investigators at the EPICOH 2017 conference held in Edinburgh, Scotland.

The Hardmetal Epidemiology Study (Epi Study) was prompted by the decision of the International Agency for Research on Cancer (IARC) in 2006 to classify tungsten carbide with a cobalt binder (WCCo) as a probable human carcinogen based on limited evidence in humans and sufficient evidence in animals that WCCo acted as a lung carcinogen. A review of the scientific basis for the IARC decision revealed significant limitations in the earlier studies of French and Swedish workers on which it was based. The Epi Study was designed to overcome the methodological limitations of earlier studies by including a comprehensive, quantitative exposure assessment conducted by the University of Illinois at Chicago (UIC), country-specific cohort mortality studies in the United States, Austria, Germany, Sweden and the United Kingdom and methods to determine if smoking could be responsible for any observed elevations in lung cancer risk.

The Epi study included 32,354 workers from several companies with 17 manufacturing sites in five countries (8 US sites, 3 German sites, 3 Swedish sites, 2 UK sites, and 1 Austrian site), each independently conducted under the direction of country-specific occupational epidemiology experts. UIC conducted an assessment of historical exposure levels to tungsten, cobalt and nickel for each of the 17 study sites. The University of Pittsburgh (UPitt) served as the coordinating center for the overall study and also performed an analysis which combined the data from each country, called a pooled analysis. This study was larger, more robust and more definitive than any hardmetal epidemiology study done to date.

A primary goal of the pooled analysis was to evaluate the relationship between the level and duration of tungsten, cobalt and/or nickel exposure and mortality from lung cancer with adjustment for potential confounding by smoking. Also evaluated were mortality rates for other cancer and non-cancer cause-of-death categories. The results of the exposure assessment, the country-specific studies and the pooled cohort analysis were presented in a series of eight online articles in the Journal of Occupational and Environmental Medicine in December 2017 (Volume 59, Issue 12). The weblink to this volume is: https://journals.lww.com/joem/toc/2017/12000. The following is a summary of the key methods and findings from the pooled analysis.

The study methodology involved evaluating lung cancer mortality risks in the pooled cohort using external mortality comparisons, where mortality rates among workers are compared to the mortality rates of the general population in the area surrounding each facility. Also used were internal mortality comparisons, where lung cancer rates among workers more heavily exposed to tungsten, cobalt or nickel were compared to workers with the lowest levels of exposure to these agents.

The pooled cohort analysis revealed no consistent evidence of elevated lung cancer mortality risks overall. No consistent evidence was found of elevated lung cancer mortality risk by demographic factors, like age at hire or sex, nor among exposure-based subgroups. Consistent deficits in lung cancer mortality were found when comparing workers

with the greatest potential for risk (eg, employed more than 5 or more than 10 years, and followed for 20 or more or 30 or more years) with workers without these risk potentials.

The analyses of lung cancer rates in relation to the duration, average intensity and cumulative exposure to tungsten, cobalt and nickel indicated that none of these agents was a risk factor for lung cancer mortality. These findings were consistent with the observation that the median average intensity of exposure to each agent (calculated across all workers in the pooled study) were well below the 2016 Threshold Limit Values (TLVs) for tungsten, cobalt and nickel, and indicate that workers exposed to these levels are not at an increased risk for lung cancer. The findings of decreased lung cancer risk estimates were unaffected by statistical adjustments for the smoking history of workers.

The pooled and country-specific results were generally not consistent with the results from the earlier epidemiology studies conducted in France and Sweden. The earlier studies revealed elevated and mostly statistically significant overall elevations in lung cancer mortality. Deficits in deaths were found in all countries except Sweden. The elevated lung cancer rate in the Swedish study was limited to short-term workers, who worked at the facilities for less than one year. Causes of death included for example cancer, heart disease, cirrhosis of liver, as well as accidents, suicides and homicides. The higher mortality is not considered to have resulted from their short time in the hardmetal industry, but instead from differences in behavior and lifestyle characteristics, or from exposures received before or after employment in the hardmetal industry. Higher mortality among short-term workers is commonly seen in similar worker studies.

In conclusion, the pooled analysis of country-specific cohort data from the Epi Study of an international study of hardmetal production workers provided no consistent evidence that work in this industry is associated with an increased risk of lung cancer, as suggested in the earlier French and Swedish epidemiologic studies. No evidence were found that duration, average intensity or cumulative exposure to tungsten, cobalt or nickel, at levels experienced by the workers examined, increases lung cancer mortality risks. No evidence was found that work in the US or EU hardmetal industry increases mortality risks from any other cause of death. The results of the pooled cohort analysis, which were consistent with the country-specific study findings, should help guide risk management efforts for workers exposed to hardmetal so that exposures are maintained below levels where increased risks may occur.

Dr Marsh's report concluded with grateful acknowledgement for the cooperation and assistance of representatives from the ITIA and the participating member companies, as well as to his co-investigators and associates in the US and Europe whose professionalism, hard work and dedication contributed to the success of the Hardmetal Epi Study of hardmetal workers:

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