Comments on

National Toxicology Program
Draft Background Document on
Cobalt-Tungsten Carbide Powders and Hard Metals

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by

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Introduction

Several international health research agencies, including the International Agency for Research on Cancer (IARC, 2006) have recently acted to label tungsten carbide (WC) with a cobalt (Co) binder (WCCo), also referred to as "hardmetal," as a probable human carcinogen. A review of the scientific basis for this decision, such as the one presented in the NTP Draft Background Document, reveals many serious limitations in the small number of occupational epidemiologic studies of Swedish and French workers on which it was based (Hogstedt and Alexandersson, 1990; Lasfargues et al., 1994; Moulin et al., 1998; Wild et al., 2000).

Specifically, serious limitations of the Swedish study of three WCCo manufacturing sites (Hogstedt and Alexandersson, 1990) include: small cohort size; very low statistical power in the Co-exposed group; lack of regional mortality comparisons; lack of internal cohort rate comparisons, incomplete job histories and lack of control for potential confounding by smoking or co-exposures. As a group, the three reported French studies lack independence as the cohort study of 10 WCCo sites reported by Moulin et al. (1998) included most of the subjects followed separately by Largargues et al. (1994) and Wild et al. (2000). The three French studies also suffered from lack of quantitative historical exposure estimates for Co, WC or WCCo, making comparisons with the results of the Swedish study difficult. Like the Swedish study, other serious limitations of some or all of the French studies include: small cohort size and low statistical power; lack of internal and regional external mortality comparisons; incomplete job histories and lack of control for potential confounding by smoking or co-exposures.

The following comments are submitted to the National Toxicology Program, Report on Carcinogens Expert Panel to inform them and the scientific community-at-large of a new, international epidemiological study of workers from the hard metal industry underway at the University of Pittsburgh and the University of Illinois at Chicago. By addressing the many serious limitations of the previous studies, the new study will enable robust and definitive conclusions to be drawn regarding the health implications of occupational exposure to Co, WC and WCCo. The background and key features of our new study are provided in the sections that follow.

Background of New Study

The new epidemiology study is actually the third phase of a 3-phase occupational epidemiology investigation of workers employed in the WC industry initiated in the early 2000's by the International Tungsten Industry Association (ITIA). Phase 1 was a feasibility study conducted by a U.S. company (BBL, Inc.) in 2006 to determine the availability and accessibility of company records needed for the main epidemiology study that comprises Phase 3 of the investigation (Schell et al., 2006). The University of Pittsburgh (UPitt) (Gary Marsh, Principal Investigator) and the University of Illinois at Chicago (UIC) (Nurtan Esmen, Principal Investigator), under a research contract with ITIA, later extended and enhanced the Phase 1 study as Phase 2 of the overall investigation.

Phase 2, conducted from October 2007 through October 2008, allowed researchers: (1) to communicate with plants directly to help clarify specific study needs; (2) to establish communication avenues with key plant personnel and enabled those personnel to prepare their facilities for inclusion in the Phase 3 study; (3) to apply different or additional feasibility criteria to the data obtained in Phase 1; and (4) to establish parameters that created the framework within which the Phase 3 study will proceed. Three of 60 United States (US) and European (EU) tungsten carbide manufacturing sites from the Phase 1 study had been closed or operations had been consolidated since the completion of Phase 1. One site not included in Phase 1 was added for a total of 58 sites evaluated in Phase 2.

Phase 2 Study - Methods and Results

UPitt and UIC developed several criteria for a candidate site to be included in the Phase 3 study, including a minimum size of 100 or more employees historically for US sites and 500 or more employees historically for EU sites. Sites were required to have been producing WCCo or WC products since at least 1980 to allow an adequate latency period for disease development. Additionally, detailed work history (WH) information was required for all employees who ever worked at the facility. The last consideration, for non-US sites, was whether vital status tracing was possible within that country. This information was gathered by UPitt via a telephone survey and/or during a site visit. Surveys were completed in April 2008. Following the surveys, UPitt and UIC

investigators conducted four US and two EU site visit trips that included a total of 18 sites during the Phase 2 study. The sites visited were representative of the candidate sites with respect to country, company and process.

The Phase 2 study concluded that a scientifically rigorous and comprehensive epidemiology study of WCCo workers is feasible and should include workers from at least 18 manufacturing sites in the US (9 sites) and EU (3 Swedish (SE), 3 German (DE), 2 United Kingdom (UK) and 1 Austrian (AT)). The Phase 3 study, which will represent multiple companies, countries and manufacturing processes, will be larger, more robust and more definitive than any WCCo epidemiology study done to date. Additionally, Phase 2 concluded that five primary exposure agents should be evaluated and compared for potential adverse health effects in the Phase 3 epidemiology study: tungsten (W), WC, WCCo, carbon black (C) and Co.

Phase 3 Study - Primary Research Objectives

The primary research objectives of the Phase 3 study are:

1. To investigate the total and cause-specific mortality experience of current and former workers potentially exposed to WCCo at multiple US and EU industrial sites that produce(d) WCCo and/or manufacture(d) WCCo products, as compared with the experience of the corresponding national and regional populations from which the workforces were drawn, with adjustment for potential confounding factors and with emphasis on malignant neoplasms of the lung.

2. To characterize as completely as possible the past and current working environment of the study members from the sites relative to work area, job title/function and potential for exposure to WCCo as well as potential co-exposures to several known or suspected human carcinogens including W, WC, C and Co.

3. To determine the relationship between level and duration of WCCo exposure and mortality from malignant lung neoplasms with analytic adjustment to the extent possible for potential co-exposures, including tobacco smoking habits, via internal adjustment with a nested case-control study or external adjustment with a Monte Carlo sensitivity analysis.

4. To provide a framework for ongoing mortality surveillance of workers potentially exposed to WCCo with and without concomitant co-exposures.

The epidemiology component of the Phase 3 study will be complemented by a comprehensive and rigorous exposure assessment component conducted by UIC (Research Objective 2 above)**.** The primary research objectives of the exposure reconstruction component are:

1. To generate scientifically sound quantitative estimates of exposure to WCCo and other potential carcinogens for all job and/or task categories on a site-specific and time-dependent basis. Average and cumulative exposure metrics will be developed and adjusted for country, company and site variability. The interaction between company and country will also be evaluated.
2. To create exposure classes for subsequent statistical analysis in the epidemiology component of the study.
3. To assess the robustness of the exposure reconstruction models employed with respect to uncertainties arising from data gaps and inherent variability.

Phase 3 Study - Proposed Epidemiologic Study Design

Multiple study sites were chosen to afford better opportunities for contrasting cohort attributes, processes, work practices and exposures; multiple sites also increase the likelihood of producing definitive and informative conclusions by increasing the statistical power and the precision of the risk estimates for detecting true excess risks overall and in relation to occupational factors. UIC and UPitt investigators will first completely ascertain the cohort of workers with potential exposure to WCCo (Research Objective 1). UIC will perform a comprehensive exposure reconstruction of manufacturing processes and will develop task and time-specific estimates of exposure (Research Objective 2). The exposure matrix will enable UPitt investigators to construct summary measures of exposure to contaminants (Research Objective 3) and enable ongoing mortality surveillance of the cohort (Research Objective 4).

The historical cohort study will provide the epidemiological platform for the proposed investigation, including a nested case-control study of lung cancer. The cohort study will focus on mortality from lung cancer and other cause of death categories

(including total mortality). Adjustment for potential confounding by smoking will occur primarily through nested case-control studies conducted in most countries (AT, SE, US or the UK) or, in DE, via external adjustment.

Phase 3 Study- Statistical Analysis Plan

Because the recommended study sites are highly diverse relative to geographic location, cohort size and cohort entry period (facility start date in most cases), we propose to approach the statistical analysis in a site-specific manner, pooling data across sites only if warranted by evidence of sufficient homogeneity. The advantage of such diversity from an epidemiological standpoint is the ability to assess the consistency of our findings across the study populations. Efforts will be made to pool data when warranted, however, as this will improve the precision of the mortality risk estimates and increase the statistical power to detect epidemiologically important excess risks. Our statistical analysis of the study data will consist of two major parts, each of which is designed to address specific objectives of the study:

Part 1 Analysis of total and cause-specific mortality patterns in relation to basic demographic and work history factors (e.g., study site, race (US sites), gender, age, calendar time, year of hire, duration of employment and the time since first employment), with focus on cancer mortality and emphasis on the implicated site of interest (lung).

Part 2 Analysis of total and cause-specific mortality in relation to occupational exposure to WCCo with analytic adjustment for potential confounding and/or effect modification by smoking and co-exposures to known or suspected carcinogens including W, WC, C and Co also with focus on cancer mortality and emphasis on lung cancer.

To provide the most unbiased assessment of lung cancer risk possible from the available study data, we have included in Part 2 a nested case-control study of lung cancer in the AT, SE, UK and US sites. In this study, we will make an intensive effort to obtain the most complete and accurate individual worker-level data on tobacco smoking habits for all cases (deaths) of lung cancer and corresponding groups of non-cases

(controls) selected from the remaining cohort members. In the DE sites, we will control for potential confounding by smoking via external adjustment.

While we plan to collect smoking information to the extent possible on all study members, these data may be incomplete. By performing this adjustment in the case-control setting we will be more likely to have complete data on smoking as most of the cases and corresponding controls will fall into the later time periods when these data are more complete. The statistical analysis of the case-control data will involve relative risk regression modeling of the matched sets with adjustment for potential confounding by smoking and co-exposures to several known or suspected carcinogens.

Phase 3 Study- Organization of Subcontractors and Collaborators

The UPitt component will be directed by Gary Marsh, Ph.D. and Jeanine Buchanich, Ph.D. UIC, under the direction of Nurtan Esmen, Ph.D. and Steven Lacey, Ph.D., will serve as a subcontractor to UPitt for the exposure reconstruction; DataBanque (DB), a Pittsburgh-based company under the direction of Susan Allen, will serve as the data processing subcontractor. The EU site investigators will be responsible for enumerating the country-specific cohorts, collecting and processing the data and conducting the vital status tracing. Following are the names and affiliations of persons who will serve as the EU co-investigators:

Austria: Manfred Neuberger, Ph.D., Professor of Environmental Health, Center of Public Health, and head of the Department of Preventive Medicine, Institute of Environmental Health at the Medical University of Vienna.

Germany: Peter Morfeld, Ph.D., Head of the Institute for Occupational Epidemiology and Risk Assessment (IERA), Evonik Services GmbH.

Sweden: Magnus Svartengren, Ph.D., Professor of Environmental and Occupational Medicine, Karolinska Institute in Stockholm and Unit Head, Environmental Medicine, Department of Occupational and Environmental Health at Stockholm Center for Public Health

England: Thomas Sorahan, Ph.D., Professor of Occupational Epidemiology, The University of Birmingham, Institute of Occupational Health.

Phase 3 Study - Projected Timeline and Budget

The proposed Phase 3 Study is anticipated to take approximately four to five years to complete. Part 1 of the Phase 3 study, which includes data collection at the participating US sites, is anticipated to begin in December 2008 or following receipt of pending funds from the State of Pennsylvania Department of Health (PADOH). Subsequent parts of Phase 3 will be started as additional funding becomes available. The PADOH has stated to UPitt their intention to provide $670,000 in direct costs for Part 1 of Phase 3 of the full epidemiology study and they have received a detailed application from UPitt for these funds. The initiation of Phase 3 Part 1 is dependent upon the receipt of the funds. Subsequent parts of Phase 3 are contingent upon procuring additional funding sources.

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