Occupational Exposure Reconstruction for Tungsten Carbide Manufacturing Workers

BY

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DISSERTATION

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This dissertation is dedicated to my advisor and mentor, Nurtan Esmen, who has provided project support and personal and professional guidance, as well as unending patience and understanding, over the many years I have been privileged to work with him. It is an honor to be his final doctoral student.

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Kathleen Kennedy

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LIST OF ABBREVIATIONS

AA	Atomic Absorption
ACGIH	American Conference of Governmental Industrial Hygienists
ANOVA	Analysis of Variance
CAS	Chemical Abstracts Service
CDA	Censored Data Analysis
CFC	Closed-Face Cassette
CI	Confidence Interval
Co	Cobalt
DNA	Deoxyribonucleic Acid
EPA	Environmental Protection Agency
IARC	International Agency for Research on Cancer
ICP	Inductively Coupled Plasma
IH	Industrial Hygiene
IOM	Institute of Occupational Medicine
IRB	Institutional Review Board
ITIA	International Tungsten Industry Association
JEM	Job-Exposure Matrix
LEV	Local Exhaust Ventilation
LOD	Limit of Detection
MLE	Maximum Likelihood Estimation
MWF	Metalworking Fluid
Ni	Nickel

LIST OF ABBREVIATIONS (continued)

NIOSH	National Institute for Occupational Health and Safety
NTP	National Toxicology Program
OEL	Occupational Exposure Limit
OFC	Open-Face Cassette
OR	Odds Ratio
OSHA	Occupational Health and Safety Administration
PEL	Permissible Exposure Limit
PPE	Personal Protective Equipment
REL	Recommended Exposure Limit
SMR	Standardized Mortality Ratio
TLV	Threshold Limit Value
TWA	Time-Weighted Average
UIC	University of Illinois at Chicago
UPitt	University of Pittsburgh
US	United States
W	Tungsten
WC	Tungsten Carbide
WCCo	Tungsten Carbide with Cobalt
XRF	X-Ray Fluorescence

SUMMARY

Quantitative exposure estimates for hardmetal workers were generated for cobalt (Co), tungsten (W), and nickel (Ni) over the time period 1952 – 2014. Exposure intervals for 69 defined job classes were calculated from industrial hygiene (IH) measurements obtained from 21 hardmetal sites in the United States (US) and Europe. Analyses of the sensitivity of the exposure estimates to measurement correction factors for closed- and open-face cassettes and total and inhalable fraction devices and to task-based differences were performed. Qualitative factors were also analyzed to determine their potential relationship to measured agent concentrations.

The levels of exposures determined for this study were similar to or lower than those previously reported for the hardmetal industry during the 1952 – 2014 study period. The exposure level estimates were not sensitive to measurement corrections up to a factor of five and task-based differences were not detected in the job class assessed. Of the 10 qualitative factors examined, American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) time period was the most influential on measured concentration.

The exposure interval estimates generated in this study provide the necessary differentiation of jobs and exposures required for the occupational epidemiological mortality studies of hardmetal workers in which they will be utilized. The difficulty of including qualitative factors in exposure reconstructions was not resolved here. However, the analyses provided insight into some possible effects of these factors on measured concentration that may be useful for other studies in terms of evaluating the appropriateness and usefulness of including such factors.

1. INTRODUCTION

1.1 Project Background

Tungsten carbide (WC) with cobalt (Co), referred to as cemented carbide or hardmetal, is WC bound with a Co matrix. Hardmetal tools are used in machining and mining operations for their hardness and wear resistance. The Co content can vary from 3 – 30 weight percent depending on the end application, and other trace elements (e.g., titanium, niobium, tantalum, nickel (Ni), chromium, molybdenum, and vanadium) may be added to the hardmetal mixture to impart specific properties (Lassner and Schubert, 1999, p. 321). Nickel may also be used as a binding agent, alone or in conjunction with Co. The processes involved in hardmetal production and manufacture have been described in detail by several sources (Stefaniak et al., 2009; Lassner and Schubert, 1999, pp. 321 – 363; Smith, 1988; Kusaka et al., 1986; Koponen et al., 1982). Figure 2, Appendix A, shows the general steps in hardmetal powder production and tool manufacture.

Occupational epidemiological studies of a set of hardmetal manufacturing plants indicated a possible association between WC with cobalt (WCCo) exposure and lung cancer (Hogstedt and Alexandersson, 1990; Lasfargues et al., 1994; Moulin et al., 1998; Wild et al., 2000); however, the small number of plants and workers included limited these findings. The International Tungsten Industry Association (ITIA), a trade association of several hardmetal companies, then examined the potential for a larger, more comprehensive study. The association retained a consulting firm to assess the possibility of conducting an occupational epidemiological study, and the consulting firm reported their initial findings to the association in 2006. The association subsequently contacted the University of Illinois at Chicago (UIC) and the University of Pittsburgh (UPitt) to further assess study potential.

Working from the initial findings of the consulting group, UIC and UPitt developed a phone questionnaire for potentially eligible study plants. Knowledgeable plant personnel answered questions regarding whether and to what extent work history and industrial hygiene (IH) records were available and what types of processes were performed at the site. Phone interviews for 58 sites were conducted by UPitt and completed in early 2008. Based upon site responses, UIC and UPitt selected plants to visit in the United States (US) and Europe to further evaluate their potential for study inclusion.

Starting in 2008, UIC and UPitt conducted site visits at 14 US and 9 European plants to review available records and observe plant operations. Twelve US plants were initially deemed suitable for study inclusion; further work history record review by UPitt restricted eligibility to eight US sites due to incomplete records from four plants. International sites in Austria (n = 1), Germany (n = 3), Sweden (n = 3), and the United Kingdom (n = 2) were also included in the study; these countries have their own Principal Investigators and shared anonymized work history and IH data with the US. The occupational exposure reconstruction component (generation of exposure estimates over time) is led by UIC, and the epidemiological and biostatistical component (mortality tracing and linkage/analysis of work histories and exposures developed by UIC) is led by UPitt.

The exposure reconstruction conducted for this project will be used in the occupational epidemiological mortality studies of US and European hardmetal workers conducted by UPitt. The main goals of this project were to:

1) Generate scientifically sound exposure estimates to Co, tungsten (W), and Ni

2) Analyze the sensitivity of the exposure estimates generated to measurement correction factors

3) Analyze the sensitivity of the exposure estimates generated in relation to tasks

4) Assess the potential influence of qualitative factors on measured agent concentrations

1.2 Aim 1

Aim 1 of this research was to develop retrospective quantitative occupational exposures to Co, W, and Ni for a cohort of hardmetal manufacturing workers covering the period 1952 (the earliest US epidemiological observation year) to 2014 (the latest European work history data collected). Reconstructing occupational exposures within an industry requires knowledge of the processes and tasks currently and historically performed (gained by conducting site visits, meeting with knowledgeable plant personnel, and examining relevant documentation) and collection of available IH measurements. Exposure reconstructions performed for the few prior occupational epidemiological mortality studies in the hardmetal industry had access to fairly limited IH data, assessed Co exposure only, and generated broad exposure classes (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990). Aim 1 included the development of an appropriate method to utilize the available IH data from the 21 European and US study plants to quantitatively estimate historical exposure to Co, W, and Ni. Aim 1 also included an analysis of the sensitivity of the estimates generated to measurement correction factors and task differences within a job class.

The need to study other groups exposed to Co along with more refined exposure assessments has been indicated (Hogstedt and Alexandersson, 1990). Exposure reconstructions in prior studies have had narrow industry representation (e.g., one country or one company included) and limitations with their exposure reconstructions (e.g., no quantitative estimates, broad exposure categories) (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990). This research developed quantitative exposure estimates to Co, W, and Ni based upon data from 21 sites representing multiple companies in several countries involved in hardmetal production and manufacturing.

This study is significant because it provided the most comprehensive cohort exposures to Co reported to date in this industry and included an assessment of W and Ni exposures. This study also provided quantitative exposure data for an occupational cohort mortality study on hardmetal manufacturing workers currently underway. It may also provide useful information to policy-making groups examining hardmetal exposures and health outcomes.

1.3 Aim 2

Aim 2 of this project identified qualitative factors of interest and evaluated whether they exerted an influence on measured Co, W, and Ni concentrations. This project contained 21 hardmetal manufacturing plants located in five countries and operated by three companies, which invites potential exposure differences related to types of operations performed, recommended exposure standards, and technological developments (e.g., improvements that occur as a process matures). While it is difficult to quantify such qualitative factors in an exposure reconstruction, they have been observed to have an effect on exposure levels over time (Creely et al., 2007; Symansky et al., 2000; 1998).

Qualitative factors are generally not considered or included in a reconstruction. If they are, it is frequently solely on the basis of professional judgment and the parameters used by the decision makers are often not clearly identified. Methods for evaluating qualitative factors were not reported in the prior hardmetal studies (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990). This aim is significant because it offers insight into potential influences on measured exposure levels arising from parameters that may not otherwise be considered or detected. The identification of such factors may also detect exposure pattern shifts that could be useful when exposure measurements are unavailable or limited.

2. LITERATURE REVIEW

2.1 Hardmetal Occupational Epidemiology

Health effects of Co exposure in humans include skin sensitization (allergic contact dermatitis), bronchial asthma, and hardmetal lung disease (IARC, 2006). The role of Co in human carcinogenesis, specifically lung cancer, is less clear. Four mortality studies on hardmetal workers have been conducted to date.

A 1990 cohort mortality study on 3,163 hardmetal production workers from three Swedish plants assessed Co exposure from 1940 – 1982 (Hogstedt and Alexandersson). Five exposure categories (0 – 4) were created based upon discussions with plant personnel, and average Co concentrations for each group were determined based upon published data from the 1950's and 1970's. Mortality analyses were reported on exposure categories 1 and 2 combined (low exposure), categories 3 and 4 combined (high exposure), or all categories combined. No one in the cohort identified as category 0 (not exposed to Co) was included (e.g., no administrative, engineering, or non-production jobs) and no smoking or other tobacco use information was gathered. Mortality analyses of the 17 lung cancer deaths for the period 1951 – 1982 showed a statistically significantly elevated standardized mortality ratio (SMR) (7 deaths, SMR = 2.78, 95% confidence interval (CI) 1.11 – 5.72) for workers with first exposure more than 20 years ago and greater than 10 years of exposure for categories 1 – 4 combined.

A cohort mortality study reported in 1994 on 709 male French workers employed for more than one year at one hardmetal site established four exposure categories (1 – 4) based on employee work histories and Co aerosol measurements taken in 1983 (Lasfargues et al.).

Smoking status (never/former/current) was determined from medical records and interviews for 69% of the deaths and 81% of all workers. Mortality analyses for deaths over the period 1956 – 1989 were performed for the four exposure categories (not exposed/low/medium/high). For the 10 lung cancer deaths observed, results showed a significantly elevated SMR for the whole cohort (SMR = 2.13, 95% CI 1.02 – 3.93) and for workers in the high exposure category (6 deaths, SMR = 5.03, 95% CI 1.85 – 10.95). In the combined medium and high groups, there was no relationship detected between lung cancer mortality and time since first employment or length of employment.

Moulin et al. (1998) performed a nested case-control study of 7,459 hardmetal workers with employment duration of three months at any of 10 French sites; this included the plant studied by Lasfargues et al. (1994) and minimum employment at this site was one year. Males and females were included. Sixty-one lung cancer cases and 180 controls were included. Smoking status (ever/never) was obtained via interview for 80% of subjects. Experts (epidemiologists, industrial hygienists, occupational doctors, and industry representatives) constructed a job-exposure matrix (JEM) with 320 job periods and assigned semi-quantitative levels (0 – 9) of exposure to Co and WC along with a frequency score (exposed <10%, 10 – 50%, or >50% of working time). The JEM was validated using 744 (264 personal, 480 area) Co measurements from 1971 – 1994; a correlation (not reported) was established between the assigned levels and the log-transformed measurement values.[1] For mortality analyses of deaths for the period 1968 – 1991, workers were grouped into four exposure categories (0 – 1, 2 – 3, 4 –

[1] While the JEM was coded for simultaneous Co and WC exposure, data only existed for Co. This is typical of IH sampling databases at hardmetal sites because there is no standard method for measuring WC alone.

5, and 6 – 9) and Co and WC exposure analyzed as maximum intensity in the work history, exposure duration at ≥ level 2, and unweighted (intensity x duration) and weighted (intensity x duration x frequency) cumulative exposure. The lung cancer odds ratio (OR) of workers with Co and WC exposures at levels 2 – 9 (low to highest exposure) versus 0 – 1 (no to very low exposure) was significantly elevated (OR = 1.93, 95% CI 1.03 – 3.62). Significant trends were found for duration of exposure (at ≥ level 2) and unweighted cumulative dose, but not for the four separate exposure categories or weighted cumulative dose.

Wild et al. (2000), making use of more complete work histories and improved mortality tracing, further evaluated one of the 10 French hardmetal sites included in the Moulin et al. (1998) case-control study. The mortality cohort included 2,216 males and 644 women employed at least 3 months from 1950 – 1992 and followed from 1968 – 1992; women were only included in the overall mortality analysis. Smoking status (ever/never) was obtained from occupational health department records and interview of former workers and determined for 66% of the cohort. The same JEM and exposure metrics from Moulin et al. (1998) for Co and WC were used, and exposures of men by workshop (7 process-related areas) were evaluated. There were 47 lung cancer deaths in the cohort; the SMR for men was significantly elevated (46 deaths, SMR = 1.70, 95% CI 1.24 – 2.26). A significantly elevated SMR was observed for men exposed at ≥ level 2 (26 deaths, SMR = 2.02, 95% CI 1.32 – 2.96). Increased SMRs were also seen for men only employed and ever employed in hardmetal production before sintering (only: 6 deaths, SMR = 2.91, 95% CI 1.06 – 6.34; ever: 9 deaths, SMR = 2.42, 95% CI 1.10 – 4.59) and for men only and ever employed in maintenance (only: 9 deaths, SMR = 2.82, 95% CI 1.29 – 5.36; ever: 11 deaths, SMR = 2.56, 95% CI 1.28 – 4.59).

The limitations of the four prior mortality studies of the hardmetal industry include small cohort sizes, few lung cancer deaths, lack of smoking or other tobacco use information, and assessment of exposures using broad classes and limited data (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990). This exposure reconstruction study was designed to address the lack of quantitative Co, W, and Ni exposure estimates in the prior studies, as well as develop a more refined job dictionary due to the relative completeness of work histories available from the current study sites.

2.2 Cobalt, Tungsten, and Nickel Health Effects

The American Conference of Governmental Industrial Hygienists (ACGIH) classifies Co as Group A3 (animal carcinogen with unconfirmed human carcinogenicity) with the potential to elicit asthma and myocardial effects and to adversely affect pulmonary function (ACGIH, 2016). Cobalt is classified by the National Toxicology Program (NTP) as reasonably anticipated to be carcinogenic based on animal studies (sufficient evidence) and mechanistic studies (supporting evidence); evidence was deemed insufficient to evaluate human carcinogenicity (NTP, 2016).

Tungsten carbide powders and hardmetals are listed by NTP as reasonably anticipated to be carcinogenic based upon limited animal study evidence and supporting mechanistic evidence (NTP, 2016). Although NTP indicated that there was evidence of human carcinogenicity of these materials, their assessment was derived from the prior epidemiological studies discussed in Section 2.1 (NTP, 2016; Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990). The methodological issues related to the prior studies were previously described (see Section 2.1); the current study by UPitt and UIC was designed to address methodological issues associated with those studies.

In their 2006 review, IARC found limited evidence of carcinogenicity in humans for WCCo (Group 2A) based upon the four prior epidemiological hardmetal studies (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990) and inadequate evidence of carcinogenicity in humans for Co alone (Group 2B) based upon two studies with Co exposures from non-hardmetal industries. The group did find sufficient evidence of carcinogenicity in animals of Co powder. While the genotoxic effects (e.g., deoxyribonucleic acid (DNA) strand breaks, gene mutations, inhibition of p53 binding, etc.) observed in animal studies (*in vitro* and *in vivo*) and human studies (*in vitro*) remain unknown, it has been proposed that Co ions may directly damage DNA through a Fenton-like process (oxidation resulting in free radicals) or inhibit repair of existing DNA damage. However, Co ions are not readily bio-available due to protein binding and precipitation. Another mechanism proposed is the reduction of oxygen in the presence of WCCo particles by electrons moving from the Co particles, which are then oxidized and become soluble. Studies have shown that WC and Co in combination are more mutagenic together than Co alone, and it has been suggested that the WCCo particles together behave like a new entity and acquire properties different from their components. (IARC, 2006)

Lower respiratory tract irritation has been noted for tungsten (ACGIH, 2016), but it has not been individually classified by IARC or NTP. Health effects observed in the hardmetal industry to date have historically been ascribed to Co in the workplace, not W (ATSDR, 2005).

Although no mechanism of action for W-induced health effects has been determined, *in vitro* experiments have shown that tungsten oxide fibers in hardmetal industries can induce hydroxyl radicals in human lung cells and *in vivo* animal experiments have demonstrated that intratracheal deposition of WC with Co (but neither alone) can induce pulmonary fibrosis (ATSDR, 2005). Even though W alone may not be considered the main etiologic agent in hardmetal-related diseases, the potential for hardmetal aerosols to induce changes to lung cells (ATSDR, 2005) and initiate lower respiratory tract irritation (ACGIH, 2016), the lack of W assessment in prior studies (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990), and the ability of the overall epidemiological study to look at all causes of mortality (cancer and non-cancer) in relation to W exposure justified the reconstruction of W exposures in this project.

Nickel in powder form may be used as a binder material alone or in conjunction with Co. Elemental Ni is classified by ACGIH as Group A5 (not a human carcinogen) and health effects include pneumoconiosis and dermatitis (ACGIH, 2016). Metallic Ni is classified by NTP as an anticipated human carcinogen based on evidence from animal experiments (NTP, 2016).

Nickel compounds are deemed human carcinogens (Group 1) by IARC based on sufficient evidence in animals and humans for Ni compounds and metal (IARC, 2012). Nickel compounds and Ni metal were not separately classified by IARC due to experimental evidence that inhaled metallic Ni dust can become bioavailable (IARC, 2012). The particle sizes of hardmetal powders, and therefore any included powdered Ni, may be similar to or larger than the fume encountered in Ni production (Lassner and Schubert, 1999, p. 324; Wang et al., 2016).

Most of the epidemiological health effects cited in the IARC monograph stemmed from Ni production (mainly smelting and refining), and it was these studies upon which the IARC classification was primarily based (IARC, 2012).

Despite differences between Ni exposures in production and Ni exposures in the hardmetal industry, powdered elemental Ni was included in the exposure reconstruction for this project because of its potential bioavailability and ensuing carcinogenic health effects, and because exposure to Ni was not assessed in prior occupational epidemiological studies of the industry (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990).

Evaluation of both W and Ni has been recommended previously. According to Kraus et al. (2005, p. 632), "To be able to evaluate the risk of cancer in the hardmetal industry, the exposure situation needs to be assessed not only for [Co] and its compounds but also for [W] and [Ni]."

2.3 Exposure Reconstruction Approaches for Occupational Epidemiology

Occupational health studies have utilized exposure information since the 1930s (Sahmel et al., 2010). Evidence of the general decline in exposures over time within manufacturing has been reported and credited to factors such as the implementation of occupational health and safety regulations designed to reduce occupational exposures, reductions in occupational exposure limits (OELs), improved ventilation, and improved process engineering (Creely et al., 2007; Symansky et al., 2000; 1998). As exposures became more controlled (i.e., lower), it became critical to accurately estimate levels experienced by workers for use in occupational epidemiological studies to decipher relationships between exposures and health effects (Esmen, 1998; Seixas and Checkoway, 1995; Kauppinen, 1994; Esmen, 1991; Seixas, 1991) for the purposes of setting regulations/recommendations and protecting workers.

One of the most common tools used in exposure reconstruction is the JEM. Its use dates back to a 1941 matrix listing occupations and hazards (Goldberg et al. 1993), and it has developed over time for use in exposure reconstruction and occupational epidemiology. Job-exposure matrices can be used in large studies where it is cost-prohibitive to determine individual exposures, and are often used in industry-specific health investigations (Goldberg et al., 1993). A basic JEM created in an exposure reconstruction for application in an occupational epidemiological study consists of groupings of workers (job classes, similar exposure groups, etc.) that may be based upon job title, job task, department, work zone, exposure potential, or other relevant parameters along with quantitative, semi-quantitative, or qualitative exposure estimates over time.

Qualitative measures generally increase uncertainty (Sahmel et al., 2010), and collapsed exposure categories (e.g., ever/never, low/high) can result in exposure misclassification (i.e., worker assignment to an improper exposure category) and a biased OR or relative risk (in either direction) in epidemiological analyses (Wacholder et al., 1991). Therefore, quantitative estimates are preferred for exposure reconstruction because confidence in the estimates obtained is improved (Sahmel et al., 2010). Quantitative estimates, which are most useful for determining acceptable plant exposure levels in regards to health effects, may be derived from IH datasets, modeling, or physical experiments recreating historical conditions. Physical experiments are usually cost-prohibitive and IH datasets may be incomplete, in which case quantitative estimates may be obtained by using available IH measurements along with some degree of modeling.

A thorough review of exposure reconstruction methods used in occupational studies and human health risk assessments by Sahmel et al. (2010) described the methods most often employed in reconstruction and provided examples of each. In addition to quantitative assessment, semi-quantitative, qualitative, and combination approaches may be used.

Semi-quantitative methods are often used in studies with limited IH measurements available. These methods utilize approaches such as extrapolation or interpolation, where unknown values are estimated using known values via regression or analysis of variance (ANOVA), estimation using models such as single-zone or near and far field, and exposure determinants such as emission rate, ventilation patterns, PPE, particle size characteristics, or personal hygiene factors to refine or modify estimates of exposure. Qualitative methods may use professional judgment or self-reported exposures to perform or refine a reconstruction. Combined methods employ measured or simulated data in conjunction with qualitative information (e.g., professional judgment) and/or semi-quantitative information (e.g., mathematical or pharmacokinetic models or questionnaires). (Sahmel et al., 2010)

It is important to note, “No single exposure reconstruction approach is effective in assessing all exposure conditions or situations” (Sahmel et al., 2010, p.803). Given the inherent variability of access to IH measurements and other pertinent information, study objectives, project timelines and budgets, and other factors, Sahmel et al. (2010) developed a framework that researchers may follow that the authors believe will help enhance exposure reconstruction consistency and comparability.

Step 1 of the Sahmel et al. (2010) framework is to define the study goals in terms of what agents will be included and what health endpoint is of relevance. Step 2 is to organize and rank the information that is available. For example, documentation of IH measurements, human resources job titles, job descriptions, exposure control and process changes over time, production rates, and other types of significant information are gathered and ranked in order of completeness and relevance to aid in the selection of a reconstruction approach. For most situations, quantitative data is most important and robust, then model estimates and semi-quantitative data, and lastly qualitative data. Gaps in relevant resources, such as lack of IH measurements, task details, and model inputs, are identified in step 3. Gaps may be resolved by a variety of methods including obtaining new data, modeling, extrapolation/interpolation, professional judgment, or revising the scope to accommodate available data. (Sahmel et al., 2010)

In step 4, the exposure reconstruction approach is selected considering the ultimate application of the estimates, exposure route, and accuracy of sampling method for the agent(s) of interest (Sahmel et al., 2010). When formulating the approach Sahmel et al. (2010) noted "classifying exposures according to the most specific exposure grouping possible is ideal" (Sahmel et al., 2010, p. 808) whether that be by job title, task, department, exposure zone, some other criterion, or a combination of criteria. Departmental classification may not be adequate for many studies, however, because multiple operations may exist simultaneously in the same department (Gamble and Spirtas, 1976). Worker classification should be objective, not subjective (e.g., based on perceived risk), and small enough to be homogenous but large enough for statistical analysis (Gamble and Spirtas, 1976).

Incorporation of probabilistic methods to evaluate the variability of the parameters used in the reconstruction (e.g. Monte Carlo analysis) comprise step 5 of the Sahmel et al. (2010) framework. Step 6 involves performing an uncertainty analysis for the reconstruction results (e.g., qualitative or quantitative sensitivity analysis). In the final step (step 7), exposure estimates are validated. Validation can be done in a variety of ways, including comparing generated models with available measurements not used in the reconstruction, comparing similar chemical/operation data to modeled estimates, and employing more than one reconstruction method for the same exposures to assess estimate quality (although it was noted that this should only be done "in the absence of better options for validation" (Sahmel et al., 2010, p. 829). (Sahmel et al., 2010)

One approach sometimes used to generate quantitative exposure estimates in exposure reconstruction is multivariable regression modeling using IH measurements and a set of variables related to the measurements and other plant conditions. For example, Greife et al. (1988) modeled ethylene oxide exposures using a regression model with 23 variables and 230 mean exposures from 14 plants grouped on year, plant, and sampling media for each location and job. Seven variables were statistically significant (year, product age, product type, product aeration, sterilizer volume, exhaust valve, and exposure category). In a comparison with data not used to build the model (50 mean exposure values from six plants), both a panel of experts and the model underestimated average exposure. More problematic, however, was that the overall exposure equation derived contained second-order and interaction terms, which makes interpreting the relationship among the seven significant variables and exposure difficult.

Regression pre-supposes that the data being used in the modeling are samples. Industrial hygiene measurements are not samples; they are happenstance measurements made without statistical design principles (i.e., not collected in a random or systematic fashion) (Esmen et al., 2007a). This is in contrast to studies that obtain random samples using experimental design. Examples include full and fractional factorial designs used in an IH study to determine significant process factors related to metalworking fluid (MWF) mist mass concentration during turning operations (Gunter and Sutherland, 1999), an IH study using two-level factorial design to examine factors affecting mass concentration and particle size during wet and dry turning (Sutherland, et al., 2000), a full and fractional factorial engineering study to investigate MWF effects during drilling (Haan et al., 1997), and an engineering study using full and fractional factorial design to elucidate conditions affecting MWF mist formation during turning (Yue et al., 1999). In studies such as these, regression may be readily utilized, if appropriate, because the criteria of random and systematically obtained samples are met.

The purpose and selection methods for IH measurements are not always clear; they may be measurements taken to problem-solve, because of convenience during monitoring (e.g., agreeable worker), due to a complaint, for compliance, or any other variety of reasons. The number of measurements taken may be decided by arbitrary factors such as available funds or a regulatory requirement. Additionally, as observed by Sahmel et al. (2010), "the accuracy of estimated exposures is limited by the reliability and robustness of the available exposure data (whether past or current), regardless of the scientific rigor of the extrapolation or interpolation method [e.g., ANOVA or regression] being used" (p. 819). In practice, constructing a regression model with numerous variables in order to determine exposures may not yield informative and meaningful results.

"All exposure estimates are approximate" (Armstrong and Oakes, 1982, p. 20), and caution must be exercised when drawing conclusions from data that was not obtained specifically for application in a reconstruction (Sahmel et al., 2010). A potential disadvantage of quantitative exposure estimates is that they could give the impression that they are more precise than they actually are (Schneider, 1991). Additionally, existing exposure variations would not be incorporated into a single average or integrated exposure estimate to the extent they should be (Esmen, 1979). Using alternative methods other than regression or correlation to determine exposures, such as the exposure interval approach employed by Kennedy at al. (2013), helps avoid ascribing statistical attributes to the available IH measurements and a level of precision to the exposure estimates that they do not possess.

Ultimately the exposure reconstruction approach selected is strongly dependent upon exposure measurement availability (Kauppinen, 1994), and it is important to be aware that exposure estimates and the processes used to generate them are "only as good as the data supporting them" (Seixas et al., 1991, p. 1037).

2.3.1 Censored Data

Environmental and occupational datasets are often highly censored, i.e., there are many measurements below the limit of detection (LOD). The difficulty with highly censored datasets (> 50.0% censored) is that one is ascribing parameters to the population that are derived from the minority of the population (i.e., uncensored points), which are selected from a known distribution, while the censored points are from an unknown distribution. The Environmental Protection Agency (EPA) has provided guidelines on the best ways to approach such datasets (EPA, 2006, pp. 130 – 136). These guidelines suggest that for < 15.0% censoring, either substitution (e.g., with 0, LOD, or LOD/2) or Cohen's method of maximum likelihood estimation (MLE) may be used. For 15.0 – 50.0% censoring levels, Cohen's method or trimmed or Winsorized means may be used. For censoring > 50.0 – 90.0%, a test for proportions is suggested. However, it is noted, "there are no general procedures that are applicable in all cases" (EPA, 2006, p. 130). Other authors give similar caution (Hewett and Ganser, 2007; Singh and Nocerino, 2002).

Hewett and Ganser (2007) and Singh and Nocerino (2002) provided simulated scenarios (e.g., varying sample sizes, censoring levels, and standard deviations) showing the results of different censored data analysis (CDA) methods so that one may compare their dataset's properties with the reported outcomes and select the most appropriate method; they also noted potential biases, which vary depending on the simulation parameters, may arise when using substitution or regression-based methods. Despite such reported biases, it is common practice to use substitution and/or regression for environmental or occupational dataset analysis.

2.3.2 Task Differences

Different tasks performed by workers may result in different exposure levels. A study of offset printing press operators was conducted to identify factors that could be measured easily and used as exposure predictors in the context of designing IH sampling surveys (Hansen and Whitehead, 1988). Repeated observations of operators (n=7) were performed and location, task, and solvent exposures (continuous monitoring in breathing zone) as well as plant ventilation were recorded on three separate days at one plant. Worker tasks were observed and timed; information on tasks was also obtained from supervisors. Time of day, task performed, location, and instantaneous solvent exposure were recorded every five minutes. Worker location and exposure were examined, and both high and low exposures were in close proximity to one another indicating location was not a determining exposure factor. Worker task and exposure were also analyzed. For all subjects the highest (peak) exposures occurred with one task (plate change, including cleaning plates and printing drums with solvents) irrespective of worker location. Regression of solvent exposure and number of plate changes showed that 57.0% of the exposure variability was explained by the number of times this one task was performed; ventilation (general airflow) was below measurement detection, and was not included as a factor in the regression.

Eduard and Bakke (1999) performed task-based assessment for two groups separately (tunnel workers and farmers) to estimate personal cumulative exposure and task-based exposure variation. Tunnel workers were separated into concrete and excavation groups based on job title. Full-shift measurements (5 – 7 hours) were taken on random days over at least two shifts to obtain at least 24 measurements on 12 workers in each job group. Personal total aerosol and respirable fraction measurements were obtained; measurements were also analyzed for quartz content. There was little variability for total aerosol and respirable faction measurements between the job groups; however, for quartz the concrete group was less homogenous than all tunnel workers combined and the excavation group was the least variable. Regression was performed to assess the effect of time spent performing various tasks on quartz exposure. In the regression model two tasks of 13 examined explained 51.0% of variability and the two tasks, demolition and "diverse concrete work" (Eduard and Bakke, 1999, p. 68), comprised 38.0% of time worked. The authors concluded that more refined groups derived from further task analysis would be warranted.

Thirteen tasks were identified for farmers in the Eduard and Bakke (1999) study. One-hour measurements were taken at 127 farms to analyze total aerosol and fungal spore concentrations. Exposures were calculated as concentration during task. Variability within farmers was greater than between farmers, and task breakdown (into 13 tasks) decreased between farmer variability. Large differences in both total aerosol and fungal concentrations by task were observed, with variability higher for all measurements combined than task group measurements.

Another important consideration is the duration of various tasks performed by a job class/similar exposure group and the potential effects on exposure. Burstyn (2009) investigated the impacts of task time uncertainty on personal exposure. Simulations were run using an existing dataset of bakery workers containing exposures to inhalable flour dust and task time observations. Five task groups and their observed task times were included. Effect of task time measurement errors (of 1, 5, 15, and 30 minutes) on task exposure ranks and the utility of a task time empirical regression model were assessed. The results showed that as true (from the simulation) and observed task time values became more divergent, the estimated exposure rate (mg dust/minute-m^3 sampled air) varied more from its true value. Exposure rates converged at 30-minute task measurement error, showing that higher exposure rate tasks were attenuated and lower exposure rate tasks were elevated. Rank order of the exposure rates was distorted when task-time measurement error reached the duration of the shortest task.

2.4 Particle Size Considerations

In any IH dataset available for use in an occupational exposure reconstruction, different aerosol fractions may have been collected by different entities. The fractions collected, the properties of the aerosols being assessed, and the processes performed in the industry of interest must all be considered in an exposure reconstruction.

Aerosol fractions are defined by ACGIH as 50.0% particle deposition at the following cut-points: inhalable ≤ 100.0 µm, thoracic ≤ 10.0 µm, and respirable ≤ 4.0 µm (ACGIH, 2016). The intent of 37 mm closed-face cassettes (CFCs) is to collect aerosol of all sizes, however this does not happen in reality (Werner et al., 1999). "Total" aerosol is therefore poorly defined, although it has been deemed to "fall under the inhalable sampling convention" because the 4.0 mm inlet on a 37 mm CFC is not size-selective (Baron, 2003, p. 184).

Across several industries inhalable mass has been found, somewhat counter-intuitively, to be greater than total mass (Skaugset et al., 2013; Werner et al., 1999; Vincent et al., 1997; Werner et al., 1996). In the 37 mm CFC, this observation has been attributed to sampler wall particle adhesion (Baron, 2003, p. 192) and inefficient capture of larger particles (less than 50.0% efficiency for particles > 20.0 µm reported) (Buchan et al., 1986). The Institute of Occupational Medicine (IOM) sampler may collect particles > 100.0 µm due to diameter (15 mm) and orientation of the sampler inlet and may also passively collect particles (Baron, 2003, p. 186 - 187; Aizenberg et al., 2001; Vincent et al., 1997; Werner et al., 1996). Additionally, IOM sampler collection efficiency increases for these larger particles as wind speeds increase (Aizenberg et al., 2001) over velocities observed in workplaces (~ 0.1 – 1.0 m/s) (Baldwin and Maynard, 1998).

Reported differences between the IOM sampler and 37 mm CFC are approximately 1.0 – 4.0 times depending on the substance measured and the process being performed (Werner et al., 1999; Vincent et al., 1997; Werner et al., 1996; Tsai et al., 1995). One study showed inclusion of the 37 mm CFC wall deposits to the gravimetric analyte yielded results similar to that obtained by the IOM sampler (Demange et al., 2002). However, this practice is not standard and has been shown to account for only about 10% of the difference between measured total and inhalable mass (Werner et al., 1999).

There are limited published data regarding the relationship between 37 mm CFCs and 37 mm open-face cassettes (OFCs), however, one paper reported a mean ratio difference of 1.3 for total aerosol between OFCs and CFCs (i.e., 30% greater mass collected by OFCs compared to CFCs) (Beaulieu et al., 1980).

2.5 Occupational Exposure Limits

2.5.1 United States

The legally enforceable OELs in the US are the Permissible Exposure Limits (PELs) set by the Occupational Safety and Health Administration (OSHA). The current general industry limits for Co and Ni are 0.1 mg/m^3 and 1.0 mg/m^3, respectively (29 CFR 1910.1000). While there is no general industry standard for W, there is a current PEL for insoluble W compounds set at 5.0 mg/m^3 for shipyard workers (29 CFR 1915.1000). The Co, Ni, and W PELs are all time-weighted averages (TWAs) based on total aerosol.

Most of the current PELs were set forth in the 1971 OSHA promulgations for general industry, and were based on existing federal or national consensus standards (Federal Register, 1971; 29 CFR). While there was an attempt to revise 212 limits and add 164 new limits in 1989 (Federal Register, 1989), the proposed updates were vacated in a 1993 appeal decision by the 11th Circuit Court of Appeals in Atlanta, Georgia (Federal Register, 1993). Total aerosol limits for Co (metal, dust, and fume; 0.05 mg/m^3), W (insoluble compounds; 5.0 mg/m^3), and Ni (metal and insoluble compounds remained 1.0 mg/m^3; revision to soluble limit only) were among the vacated standards (NIOSH, 2016a). Because more information has been gathered since the 1970s about many of the regulated substances, OSHA recommends that more stringent industry guidelines be followed in order for worker health to be adequately protected (OSHA, 2016).

The recommended standards set by ACGIH are the threshold limit values (TLVs), and are often used by companies preferring more stringent guidelines than those provided by OSHA. The TLVs for Co, W, and Ni have undergone several changes since their initial adoptions.

The TLV for Co (total aerosol) was adopted in 1963; the 0.5 mg/m^3 level was in effect until 1967. From 1968 – 1986, the Co limit (total aerosol; metal, dust, and fume) was 0.1 mg/m^3, and decreased to 0.05 mg/m^3 from 1987 - 1994. The current TLV for Co (total aerosol; elemental and inorganic compounds) of 0.02 mg/m^3 has been in effect since 1995. (ACGIH, 1986 – 2016; ACGIH, 1991)

The TLV for W (total aerosol, insoluble compounds) of 5.0 mg/m^3 was in effect from 1969 – 1998. From 1999 to present, the 5.0 mg/m^3 limit still applies, but is defined as total aerosol, metal and insoluble compounds. (ACGIH, 1986 – 2016; ACGIH, 1991)

In 1966, the 1.0 mg/m^3 TLV for Ni (total aerosol, metal) was enacted and was in effect until 1973. From 1974 – 1997, the limit remained the same but was defined as total aerosol, metal and inorganic compounds. From 1998 to present, the Ni TLV of 1.5 mg/m^3 pertains only to the inhalable fraction (metal and elemental). Other changes in 1998 included limits for soluble Ni (inhalable fraction; 0.1 mg/m^3) and insoluble Ni (inhalable fraction; 0.2 mg/m^3), however, given the use of powdered Ni as the binder in hardmetal production, the metal/elemental limit would be most applicable. (ACGIH, 1986 – 2016; ACGIH, 1991)

States may choose to enact standards that are stricter than OSHA's PELs. Of the eight states containing the initially included 12 plants, only two states (one with a plant included in the final set of eight sites in the epidemiological analyses and one with no included plant) adopted guidelines more stringent than OSHA; the remaining states followed federal guidelines. Both of these states (Michigan and Tennessee) enacted a Co (total aerosol; metal, dust and fume) limit of

0.05 mg/m^3, a W (total aerosol; insoluble compounds) limit of 5.0 mg/m^3, and retained the 1.0 mg/m^3 federal limit for Ni (total aerosol; metal and insoluble compounds) (TDLWD, 2002; MIOSHA, 2013). While the Co limit is stricter than the OSHA PEL, these three adopted state limits are not more conservative than the TLVs.

There is a Recommended Exposure Limit (REL) for WC (total aerosol) set by the National Institute for Occupational Health and Safety (NIOSH). It is based on the Co content exceeding 2.0%, which, although impossible to know for each formulation produced/used in all 21 study plants, is likely to be above 2.0% the majority of the time. The standard states that in this case, the REL is 0.05 mg/m^3 Co (NIOSH, 2016b); this is the same as the current Co TLV. The REL for WC with Ni binder is 0.015 mg/m^3 (10-hour TWA) (NIOSH, 2016b); however, since Ni is used less frequently as a binder, and sometimes in combination with Co, this standard would be difficult to apply as intended (i.e., based on known identity and quantity of binding agent). In 2016, ACGIH adopted a hardmetal TLV with a recommended level of 0.005 mg/m^3 (as Co, thoracic fraction) for WC and hardmetals containing Co (ACGIH, 2016).

2.5.2 European Countries

The OELs for the European countries are summarized in Table VI, Appendix B. Information on the history of the OELs came from several sources and is provided in the table. The details were difficult to trace and should be considered informative rather than authoritative. The values are similar to or less restrictive than the TLVs, however, the current Ni TLV (1.5 mg/m^3; ACGIH, 2016) and the United Kingdom (Great Britain, specifically) limit (0.5 mg/m^3)

are based on the inhalable fraction while the other countries' limits (0.5 mg/m^3) are based on total aerosol.

2.6 Qualitative Factors

In many occupational health studies, exposures over time have been determined by limited data and expert opinion (Esmen, 1991; Seixas et al., 1991) and factors potentially affecting exposure were not often included in a systematic manner. For example, the study of hardmetal workers by Hogstedt and Alexanderson (1990) noted that the authors considered changes in local exhaust ventilation (LEV), use of PPE, and changes in work processes but did not provide details on how these factors were considered or how they were incorporated into or influenced the resulting exposure estimates.

Statistical modeling can be employed to determine predictors of exposure (Seixas and Checkoway, 1995) and this has been performed in some occupational studies. Studies by Teschke et al. (1995) and Woskie et al. (1994) collected exposure measurements specific to their interests. The situation in Hallock et al. (1994), where extant data was used, is more common in exposure reconstruction. Though existing measurements are not generally taken in a random or systematic way (i.e., not samples), use of methods such as regression or ANOVA to look at trends or impacts of factors on measured concentrations, rather than to strictly define an exposure relationship, can be informative.

A 1995 study by Teschke et al. measured personal Co and chromium exposures among WCCo and stellite (a superalloy with chromium and more Co than WCCo) saw filing maintenance workers in eight Canadian lumber mills and sought to elucidate factors contributing to the observed exposures. Worker activities were directly observed and recorded every 10 minutes. The factors included activity (considered *a priori*), location (within 5 feet of activity), job title, day and month of sampling, time smoking, and other activities not considered *a priori*. A stepwise multiple regression modeling approach was used, which included activity and location first (Group 1) followed by inclusion of job title (Group 2) to significant Group 1 variables and the remaining factors (Group 3) to significant Group 1 and 2 variables. Both dichotomous and continuous forms of Group 1 variables were examined. Chromium and Co in MWF was analyzed in bulk samples and factors of interest included type of metal (WCCo, stellite, knife and saw steel), task/operation, and LEV effectiveness (categorized as good/fair/poor/none by visual inspection of smoke tube tests and measured capture velocities). In the dichotomous model, higher Co exposures were found to be associated with time spent near wet and dry grinding and higher chromium exposures with knife grinder job title and time spent near stellite and saw steel heating. Significant continuous Group 1 factors were time spent within 5 feet of a wet carbide grinder for Co and time spent within 5 feet of wet knife grinding for chromium. Type of metal was significant for MWF analysis of Co and chromium, with mean Co concentrations about an order of magnitude higher for WCCo than stellite grinding machines. Chromium was highest in stellite grinder MWF. Interestingly, only the task of knife grinding and not stellite grinding was associated with higher chromium air measurements; the authors proposed factors other than MWF concentration were involved.

Data collected for a respiratory morbidity and mortality study of MWF-exposed workers allowed the examination of factors contributing to MWF exposure by Woskie et al. (1994).

Personal measurements were taken using a two-stage impactor. For a subset of 309 automotive manufacturing workers performing a variety of machining operations, the categorical factors examined included plant (3 levels), MWF type (6 levels), degree of machine enclosure (3 levels), machine type (8 levels), and LEV (2 levels). Effectiveness of LEV was not assessed. Ordinal factors included the year the machine was built, outdoor temperature, indoor humidity, and worker distance from MWF. All factors were evaluated by an analysis of covariance model across three particle size fractions (> 9.8 μm, 3.5 – 9.8 μm, < 3.5 μm). The full models for all three size fractions were significant, but the significant factors varied among fractions. For example, LEV was significant for the smallest size fraction but not the other two. Machine type, MWF type, outdoor temperature, and indoor humidity were significant among all three fractions. The authors had hypothesized different significant factors for the largest and smallest size fractions due to particle behavior and performed a stepwise regression procedure to determine which factors contributed most to the models. For particles < 3.5 μm, plant was the most important factor, followed by machine type. Machine type was most important for particles > 9.8 μm, followed by MWF type and an interaction term for MWF and machine types. A baseline work area was defined using the most typical factor levels and by varying only one factor the effects on estimated exposure were examined. The highest concentrations of the largest particles were affected by straight MWFs and enclosures, while the smallest particles were affected by straight MWFs, plant, and LEV.

Another paper on MWF exposures in the automotive industry by Hallock et al. (1994), and related to Woskie et al. (1994), examined the effects of four variables on MWF concentrations. Existing measurements taken over the period 1958 – 1987 were obtained from three plants. Categorical factors included MWF type (3 levels), operation performed (3 levels), plant (3 levels), and time period (4 levels). Factors were evaluated through an ANOVA model and Tukey's test for multiple comparisons between factor levels. In the final ANOVA model plant was reduced to two levels and time period to three levels. All factors were significant with significant differences observed between the two plant levels, among certain levels of MWF type and time period, and among all operation levels. Separate ANOVAs were run for operation levels (grinding, machining, and assembly). These were significant overall with significant differences found for time period in grinding and machining. The study also examined differences between the two primary sampling and analytical methods used; these were not included as factors in the model because the differences observed were minimal. Engineering controls were assessed generally via a subset of measurements taken before and after implementation. The changes detected were of the same order of magnitude seen pre- and post-1970, however this factor was not included in the model due to the small number of before and after measurements.

3. METHODS

3.1 Job-Exposure Matrices

In this study, JEMs were constructed for Co, W, and Ni. The JEMs consisted of job dictionary classes and the exposure estimates over time generated from the available IH measurements. While there are concurrent exposures to, depending on the process step, carbon black, WC, and WCCo, there were no measurements specifically for these compounds, therefore they were not considered individually.

3.1.1 Job Dictionary

Because UIC performed the exposure reconstruction component of the overall mortality study and not the epidemiological and biostatistical component, all work history information used by UIC was anonymized. Anonymized work history line combinations were generated from work history records. Work history records were collected and abstracted by UPitt for the US sites; European investigators performed this task for their study sites. The work history records included all jobs held by each individual in the cohort over time. After collection of US work history records by UPitt, UIC received anonymized unique work history line combinations. These data lines were based upon the following fields: job title, job code, grade, department title, department code, division (larger group; e.g., mining tools), plant, location name (usually, but not always, the same as plant), and location code.

In contrast to defining job classes using available measurements as done in the Lasfargues et al. study (1994), job dictionary classes were formed prior to analyzing the IH data based upon familiarity with plant operations and worker tasks, consideration of potential exposures, and review of anonymized work history line combinations. European investigators contributed to job class construction to accommodate their plant-specific operations. The job dictionary classes were combined as warranted based upon the subsequent IH data analyses.

3.1.2 Industrial Hygiene Data

As is often encountered in occupational exposure reconstructions, there was limited IH data available for some operations and years. Therefore, due to the similarity of operations across countries, companies, and plants, all IH data from the initially eligible 12 US plants along with the IH data collected from the nine European plants were used in the reconstruction. The intent of this approach was not only to provide a greater number of IH measurements overall for generating the exposure estimates, but also the ability for the same estimates to be applied to planned cohort mortality analyses of all US and European workers combined.

All electronic and hard copy IH data records collected from the 21 US and European plants were abstracted into an Excel database by the country-specific investigators. Appendix C shows the fields contained within the database; these fields were selected based upon study-specific needs and published recommendations for exposure database construction (Rajan et al., 1997; Joint ACGIH-AIHA Task Group, 1996). A field for job class designation by the country-specific investigators was included so that non-English IH data could be more easily utilized for the exposure analyses. Because personal samples are better representative of worker exposure than are area samples (Ramachandran, 2005, p. 71; Esmen and Hall, 2000), personal samples were used in the exposure reconstruction.

3.1.3 Lognormality

Due to its right-skewed characteristics, most environmental data are best represented by a lognormal distribution (Esmen and Hammad, 1977). The IH dataset was tested for lognormality using the Ryan-Joiner test, which is a correlation-based test. Measurement concentrations given as less than a LOD value were included as ½ the LOD for this test.

3.1.4 Hierarchical Exposure Estimation Approach

The important parameter in epidemiological studies is to obtain a valid measure of exposure ranks rather than physically defined absolute exposure levels. Exposures, in an epidemiological context, are not specific doses for specific individuals, but instead a relative ordering system using “a physical “measurement” rubric for convenience” (Esmen et al., 2007b, p. 256). With the epidemiological application of the exposure estimates generated for this study in mind, the objective of the IH data analysis was to generate median yearly exposures for each job class.

In order to generate the median yearly exposures, the presence or absence of significant time trends had to first be determined. The measurements were sorted by agent, process/job class, and year. At least 10 data points, of which at least five were not censored (below the LOD), were required for each “year” category so that the overall censoring level for each year category was ≤ 50.0%. To help lessen the likelihood that trends would be detected by chance, time trend analysis required five valid year categories.

Potential biases may arise when estimates for highly censored datasets are generated using substitution (e.g., replacement of censored values with zero, LOD/2, LOD/$\sqrt{2}$, or the LOD) or regression-based methods (Hewett and Ganser, 2007; Singh and Nocerino, 2002). Therefore, each year category was analyzed by CDA, using MLE of censored data as described by Cohen (1991, pp.96-105), in Excel to determine the year category's median exposure value. Regression was then performed in Minitab 17 (Minitab, 2010) on concentration (median) over time (years) to determine the presence of any time trends. If no significant time trend was detected, or there was insufficient data to meet the specified requirements for time trend analysis, then all available data for a job class was analyzed using CDA to generate an overall job class median applicable to all study years 1952 – 2014, where 1952 is the earliest US epidemiological observation year and 2014 is the latest year of European work history records collected.

Figure 1 summarizes the hierarchical approach that was used for the analysis of the available IH measurements in order to generate median yearly exposure estimates for each job class. Exposure intervals were defined in an iterative process. After CDA was performed for several job classes, the resulting estimates were used to define intervals at convenient bandwidths. Job classes were then assigned to the corresponding interval either annually (for significant time trends) or over all study years (for non-significant time trends).

3.1.5 Sampling Time

One issue with IH data is varying sampling times, which arises from the combination of short task-based measurements (a few minutes to a few hours) and full-shift measurements (from

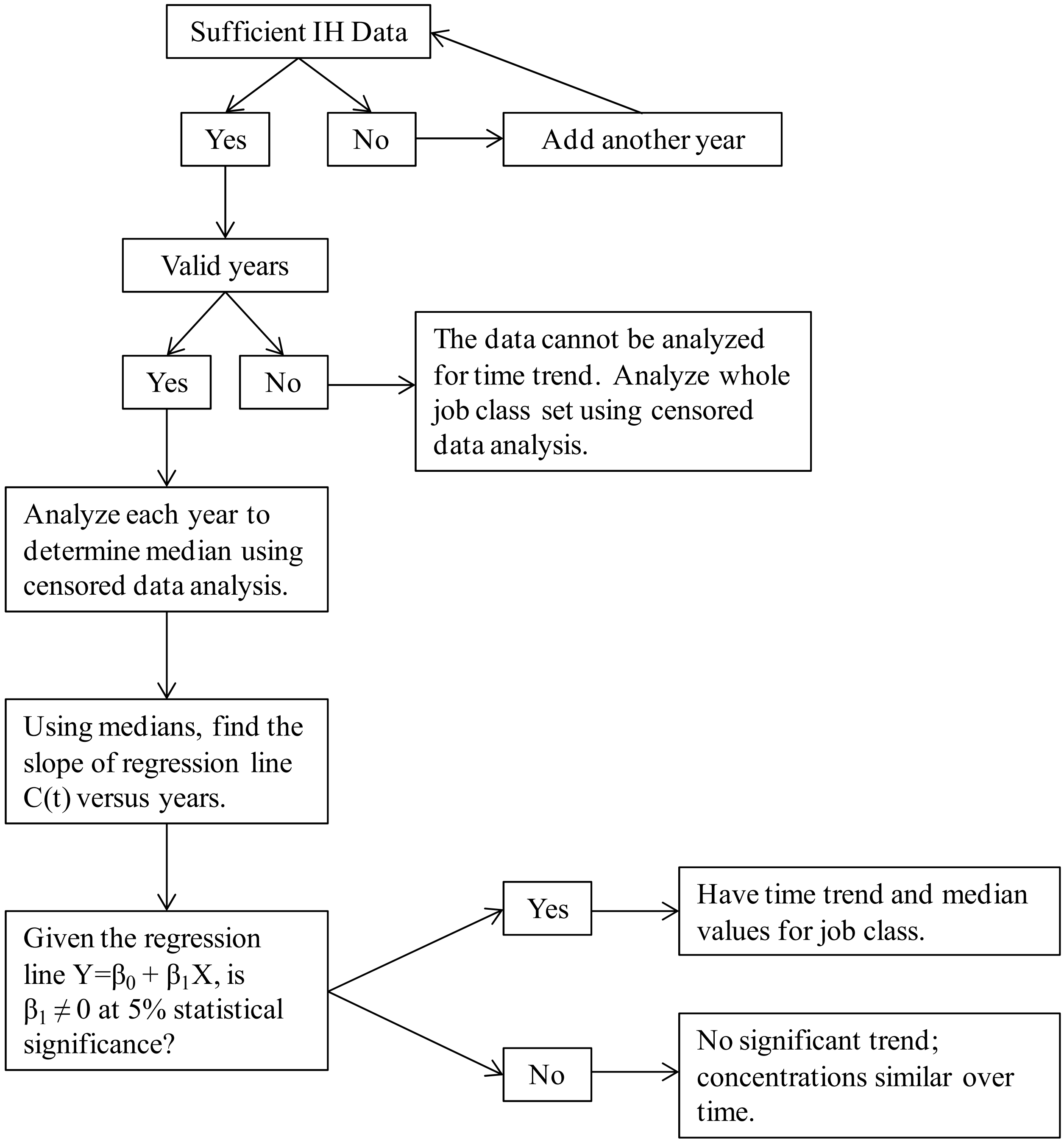

Figure 1. Hierarchical approach used for the analysis of industrial hygiene measurements.

a few to eight hours or more) in the dataset. Task-based measurements are generally collected for purposes other than determining exposures across an entire shift, e.g., to assess high exposure tasks, to evaluate the function of an installed or repaired ventilation system, or to assess exposures from a new or modified process. Tasks that are routinely performed and result in "peak" exposures would be monitored in workers' full-shift measurements. Because the goal of the study was not to quantify peak exposures specifically, but rather to generate exposure estimates reflective of full-shift conditions encompassing all tasks performed, task-based measurements were excluded from the IH data analyses.

In order to assess whether or not non-task based measurements of varying duration could be combined in the exposure analyses, it was necessary to examine the relationships of sampling time to year of measurement and to reported concentration. These relationships were examined by Pearson's correlation in Minitab 17 (Minitab, 2010) to determine if measurements taken in earlier study years were of significantly shorter duration than in later study years and if shorter duration measurements had significantly higher concentrations than longer duration samples.

Because sample duration effects may depend upon job class (Sorahan and Esmen, 2004), Co was examined overall and for several separate job classes; W and Ni were examined for one job class each. There were measurements in the Austrian dataset that listed sampling times of 480 minutes for full-shift samples instead of the precise sampling times. Due to the uncertainty surrounding these sampling times, Austrian measurements were excluded from the sampling time evaluations.

3.1.6 Particle Size Fractions

Because different countries in this study utilized different sampling devices to collect measurements, a determination regarding the relationship between those devices and the fractions collected needed to be made before beginning the exposure analyses. Generally, the US, Austria, and Sweden collected total aerosol, United Kingdom collected the inhalable fraction, and Germany collected both the inhalable fraction and total aerosol. The most common devices used were CFCs and OFCs (Sweden only) for capturing total aerosol and the IOM sampler for capturing the inhalable fraction.

While there was no particle size-specific data found within any countries' collected IH data, a limited set of measurements was obtained from one study plant. The data included cascade impactor and particle counting measurements for several operations. The data was used to calculate the mass and count median aerodynamic diameters for the measured operations using the procedure described by Hinds (1986; pp. 45 – 61). Additionally, data on total aerosol and inhalable fraction parallel sampling at Swedish study plants by the Swedish researchers has been published (Klasson et al., 2016).

3.1.7 Exposure Estimate Sensitivity

Because of the different sampling instruments used to collect measurements (primarily inhalable samplers, CFCs, and OFCs), a check of the sensitivity of the exposure estimates to changes related to these instruments was performed. Four job classes were tested using adjustments to personal Co measurements under four conditions based upon differences between inhalable and total aerosol samplers and between OFC and CFC samplers reported in the literature (Werner et al., 1999; Vincent et al., 1997; Werner et al., 1996; Tsai et al., 1995; Beaulieu et al., 1980): (1) a correction factor of 1.5 applied to inhalable measurements (i.e., inhalable value * 1/1.5, or a reduction of 33.0%); (2) a 3.0 correction factor applied to inhalable measurements; (3) a 3.0 correction factor applied to inhalable measurements in conjunction with a 30.0% reduction applied to OFC measurements; and (4) a 5.0 correction factor applied to inhalable measurements.

3.2 Task-Based Exposure Estimates

Due to the greater number of Co measurements overall, the task-based exposure estimate comparison was performed only for Co exposures. To qualify, there must have been more than one task performed by job class members and those tasks must have been clearly differentiable and indicated in the IH measurements (e.g., specified in the written notes, job title, department, or elsewhere). After reviewing the available data, the best job class candidate (i.e., tasks clearly identified and no task crossover with other job classes) was job class 4, Trades.

As for the general exposure reconstruction, personal measurements for total aerosol or the inhalable fraction with values, or less than the LOD, present were included. There were 228 measurements for job class 4, Trades, and they were 13% censored. Measurements were categorized into four task categories: (1) Cleaning (n=49); (2) Maintenance (n=103); (3) Tooling (n=31); and (4) Warehouse (n=45). Each task category was then analyzed according to the hierarchical approach and CDA methods previously described (see Section 3.1.4). Due to lack of details regarding task times, equal task time distribution was assumed. Once the medians for all four tasks were obtained, they were summed and divided by 4 (the number of job class tasks) to generate a class median.

3.3 Qualitative Factor Assessment

3.3.1 Included Factors

The factors identified and included in the occupational studies discussed in Section 2.5, while providing insight into possible exposure-influencing parameters, were specific to those investigations and all were not applicable to this study. This project used extant IH data and therefore had to rely on what was present in the measurement records.

While the potential for plant-level exposure variations exists due to factors such as LEV and respirator use, this type of information was absent from the majority of personal IH measurements. Inclusion of LEV as a factor would be difficult considering there are 21 plants among three companies that installed control technologies at varying times; it would be a guess as to whether LEV was on a particular machine that a measured worker was using during a specific year and whether the system was working properly. Only 18% of personal Co, W, and Ni measurements provided details on LEV or other control devices. The same argument can be made for PPE. Its use is rarely noted in the records; 9.0% of all personal Co, W, and Ni measurements indicated respirator use. When respirator use was indicated, it would be total speculation about whether the employee was issued the correct device, the device was fitted and maintained properly, and the device was used over the entire period of contaminant generation during the task performed. Thus, LEV and PPE were not considered as factors in this study.

Different factors were found to influence concentrations of different particle sizes (Woskie et al., 1994). Although it is known generally in this study what particle sizes are generated by a few specific processes and encountered overall, particle sizing is specific to the hardmetal powder grade produced and its end use application. Therefore, it was not possible to include a particle size factor more refined than total aerosol or inhalable fraction.

The qualitative factors included in this project were:

1) Country (5 levels: US, Austria, Germany, Sweden, United Kingdom)
2) Company (3 levels: 1, 2, 3)
3) Plant (21 levels)
4) Plant type (3 levels: manufacturing, powder mixing/blending and manufacturing, powder production and manufacturing)
5) Age of facility (2 levels: older or younger than median plant start year 1960)
6) Major job class category (3 levels: background/intermediate, manufacturing, powder production and handling)
7) Production phase (3 levels: background/intermediate/no hardmetal powder or part exposure, pre-sintering, post-sintering)
8) Particulate fraction (2 levels: total aerosol, inhalable fraction)
9) Measurement analysis period (3 levels: 1965 – 1991, predominantly atomic absorption (AA); 1992 – 1999, mix of methods including AA, inductively coupled plasma (ICP), and X-ray fluorescence (XRF); 2000 onward, predominantly ICP)
10) TLV time period (6 levels; based upon time spans by year of the recommended limits in effect for each agent)

Table VII, Appendix D, lists the factors, coding levels, and corresponding sample sizes for each level.

The information required about the factors was obtained from the IH measurements, investigator site visit notes, and/or plant contacts. Most of the factors considered are self-explanatory, however the rationale for (5), (9), and (10) should be specified.

Age of facility was included because newer plants may have lower exposures during the same time period as older plants. This could be due to easier start-up/implementation of control technologies (compared to improving and retrofitting older machines and ventilation systems) or technological process advancements (which could be more difficult to integrate into existing production systems than new ones). The median plant start-up age was used as the break point.

Instead of including all sampling material and analysis method combinations, it was possible to capture major differences by determining periods when there was an obvious shift from one type of method to another. All three agents were analyzed using the same methods; 81% of personal measurements provided method information. For those measurements with details provided, the number and percentage of measurements by year and sampling method were tabulated (see Table VIII, Appendix E) and years were broken into time periods based upon the predominant method or mix of methods used. All samples, regardless of analysis method details being included, were then assigned an analysis period. This approach is similar to other studies where sampling method itself was not categorized ((Teschke et al., 1995; Hallock et al., 1994; Woskie et al., 1994) but sampling time periods were evaluated (Symanski et al., 1998).

Variations in observed exposures may be attributed to changes in OELs over time. In the 543 industrial datasets with downward exposure trends examined by Symanski et al. (1998), effects of ACGIH TLV reductions were found (25% of datasets had one ACGIH reduction and 24% had two or three). Rather than looking at the number of reductions, which are constant for each agent, the factor can be broken into time periods based upon maximum recommended concentrations.

As noted in Seixas and Checkoway (1995), although one may want to include as many dimensions as possible in an exposure data matrix, selections must be made considering the data available and so that the resulting information is meaningful to the experience of the study group. They also point out that there may be, in practice, a limit to the number of categories included in statistical modeling due to the number of parameters that would need to be estimated. For these reasons, only the 10 factors and their corresponding levels described above were included.

3.3.2 Factor Analysis

All personal IH measurements used to generate the exposure estimates were used in the qualitative factor analysis. Each measurement was coded for the 10 factors according to the levels described in Section 3.3.1. To test the null hypothesis (H_O) that all factor levels have equal effects on agent concentrations against the alternative hypothesis (H_A) of unequal factor level effects, one-way ANOVA tests were performed for each factor individually in Minitab 17 (Minitab, 2010). All personal measurements of all agents combined were used for each factor test to determine the factors' potential impact, if any, on measured concentration.

The dataset for all three agents contained 8,336 personal measurements and was 18% censored. For measurements with concentrations below the LOD, substitution with LOD/√2 was used. The selection was based upon the results in Hewett and Ganser (2007). Simulation type I (1-50% censored, n = 20 – 100), scenario type II (single lognormal distribution, three LODs) was the closest match of the simulations presented in Hewett and Ganser (2007) to this dataset. For simulation type I/scenario type II, substitution of the LOD with LOD/√2 yielded the lowest root mean square error, which is defined by Hewett and Ganser (2007) as "an estimate of the overall accuracy (i.e. overall imprecision) [of the method], which is a function of both bias and precision" (p. 612).

3.4 Institutional Review Board Approval

The feasibility phase of the study was approved under UIC Institutional Review Board (IRB) Protocol #2007-0693; all other phases of the study were approved under IRB Protocol #2008-0949 (see Appendix F). The UPitt and European components were covered by their respective approval entities.

4. RESULTS

4.1 Job-Exposure Matrices

4.1.1 Job Dictionary

The job dictionary classes included production workers as well as administrative, engineering, laboratory, and other non-production workers. Table IX, Appendix G, shows the number of individuals in each job class and the number of working-years the individuals contributed to each class. Because a worker may be in more than one class over time, the job class metrics in Table IX, Appendix G, do not directly match the epidemiological cohort size and follow-up observation period. Additionally, UPitt detected some anomalies with hire and termination dates in the work history records of four US plants. Therefore, after UPitt conducted a more thorough review of those plants' records, they determined that the records were incomplete and therefore these four plants were excluded from Table IX, Appendix G, as well as epidemiological analyses performed by UPitt.

4.1.2 Sampling Time

Figures 3 – 9, Appendix H, show the results for sampling time versus year of measurement. Of the agent and job class combinations examined, the highest Pearson's correlation coefficient ($|\rho|$) for sampling time versus year of measurement was for personal Co measurements taken during powder milling and spray drying operations (job class 32; $|\rho|$ = 0.567; see Figure 7, Appendix H). All other values were lower and ranged from 0.090 – 0.195.

Figures 10 – 14, Appendix I, show the results for measured concentration versus sampling time. The highest $|\rho|$ detected was for personal W measurements taken during pressing ($|\rho| = 0.427$; see Figure 13, Appendix I). All other correlation values were lower, ranging from 0.09 – 0.195.

Figures 3 – 14, Appendices H and I, indicate no significant relationship between year of measurement and sampling time (i.e., there were not shorter sampling times in earlier years compared to later) and no significant relationship between sampling time and concentration (i.e., shorter duration samples did not have significantly higher concentrations than longer duration samples). Therefore, all personal non-task based measurements from all years and all sampling time durations were eligible for inclusion in the exposure analyses without correction.

4.1.3 Particle Size Fractions

Cascade impactor data showed that the mass median aerodynamic diameters of the sampled particles were small (< 3.5 μm) for total aerosol and the Co and W components; count median aerodynamic diameters were even smaller (see Figures 15 – 18, Appendix J).

Although production of special ultrafine and ultracourse hardmetal grades is possible, the common range of particle sizes for WC powder has been reported as 0.15 – 12.0 μm (Lassner and Schubert, 1999, p. 324) and for Co binders as 1.0 – 5.0 μm (Lassner and Schubert, 1999, p. 344). The mass and count mean aerodynamic diameters calculated here agree with size ranges reported within the industry. While there was no particle size data available for Ni, sizes are expected to be in the same range as that reported for WC powder as a whole and likely closer to the sizes reported for Co.

Klasson et al. (2016) reported an almost 1:1 relationship between inhalable and total Co stationary area measurements (Spearman's correlation coefficient $\rho = 0.893$). The highest correlation in their parallel sampling was between total Co aerosol and Co PM_{10} (particles with aerodynamic diameter ≤ 10.0 µm) (Spearman's $\rho = 0.945$). Correlations were not reported for personal measurements, however, the area results indicate that mass-based differences between simultaneously measured total and inhalable Co in this industry is small, and that the majority of the particles measured are below the threshold where one would expect to see collection efficiency issues between total and inhalable samplers (i.e., at approximately 20.0 µm).

Based upon the available data specific to this study and the reported literature, the determination was made that it was justifiable to use both total and inhalable measurements without correction because sampler collection differences become pronounced at much larger particle sizes than observed here.

Exposure estimates relating to the respirable size fraction were not pursued due to limited respirable data overall and the limited number of processes/tasks measured (n=126 for all Co, W, and Ni respirable measurements; n=67 for all personal Co, W, and Ni measurements taken across 9 job classes).

4.1.4 Industrial Hygiene Data

4.1.4.1 Inclusion Criteria

Based upon the sampling time and particle size fraction results, the parameters for IH measurement inclusion in the exposure estimate calculations were:

1) Personal measurement

2) From one of the 21 study plants

3) Total aerosol or inhalable fraction

4) Non-task based measurement

5) Any sampling time duration

6) Any year for Co and Ni measurements

7) Any year after 1985 for W (GE only)[2]; all years for other countries

8) No note indicating a potential issue or error with measurement (e.g., lab note, pump fault)

9) Measurement concentration given as a value or less than (<) a specified value

10) Job class number assigned by country-specific investigators

While four US plants were excluded from the epidemiological analyses conducted by UPitt due to incomplete work history records, due to similarity of work processes across plants, companies, and countries, the IH measurements from these four facilities were retained and included in the exposure estimate calculations.

[2] The German investigators determined that there was a potential issue with German W measurements taken before 1986, therefore the decision was made not to include these in the analyses. There were no personal German W measurements prior to 1986 in the database, thus the resulting exposure calculations presented here were unaffected.

4.1.4.2 Lognormality Tests

The personal measurements used in the exposure estimate calculations based upon the inclusion criteria were tested for lognormality in Minitab 17 (Minitab, 2010) using the Ryan-Joiner test at $\alpha = 0.05$. All agents individually and cumulatively were graphically and statistically lognormal, with all Ryan-Joiner correlation values > 0.9 and all p-values < 0.01 (see Figures 19-22, Appendix K).

4.1.4.3 Description of Measurements

Table X, Appendix L, shows the number of personal IH measurements meeting the inclusion criteria by agent, particle fraction (total aerosol or inhalable fraction), and country. The time periods covered by the measurements and the percent of measurements censored are also included.

Table XI, Appendix M, shows the number of personal Co IH measurements meeting the inclusion criteria by job class. Shown are the numbers of total (total aerosol plus inhalable fraction), inhalable fraction, and OFC measurements as well as the percent censored of each. The same information is shown for the included personal W and Ni measurements in Table XII, Appendix N, and Table XIII, Appendix O, respectively.

4.1.5 Exposure Intervals

The formation of the exposure intervals occurred in an iterative process whereby CDA was used to calculate exposure estimates for several job classes (with and without time trends) in order to establish a logical and convenient interval width. Table I shows the defined exposure intervals used for Co, W, and Ni. The interval midpoint is the value used in the JEM for the epidemiological exposure calculations.

TABLE I

EXPOSURE INTERVALS

Interval	Interval Width (mg/m^3)	Interval Midpoint[a] (mg/m^3)
0	0 (Outside plant)	
1	< 0.0001	
2	0.0001 - < 0.0005	0.0003
3	0.0005 - < 0.001	0.00075
4	0.001 - < 0.005	0.003
5	0.005 - < 0.01	0.0075
6	0.01 - < 0.05	0.03
7	0.05 - < 0.1	0.075
8	0.1 - < 0.5	0.3
9	≥ 0.5	

[a]Interval midpoint is the numerical value used in the job exposure matrix.

4.1.6 Time Trend Testing

Job classes with sufficient data according to the hierarchical approach presented in Figure 1 were tested for the presence of time trends. Those classes without sufficient data were analyzed as a set. Table II shows the resulting Co, W, and Ni exposure intervals for all job classes with and without sufficient data for time trend testing. Where time trends were tested, the corresponding p-values (for non-significant trends) are shown. Among the three agents,

TABLE II

TIME TREND TESTING AND EXPOSURE INTERVALS BY JOB CLASS

Job Class Number	**Job Class Group**	**Co Exposure Interval**	**W Exposure Interval**	**Ni Exposure Interval**
	Background and Support Operations			
0	Background	3	4[a]	3[a]
1	Laboratory/Research & Development	NS (p= 0.393); 4[b]	7	4
2	Supervisory	4	5	4[a]
3	Engineering	4	5	4[a]
4	Trades	NS (p=0.680); 5	8	5
5	Material handling	4	4	4
6	Assembly	4[a]	4	4
7	Mark/pack	4	4	4
8	Inspection	4	4	4
	General Production Operations			
9	Powder weigh	NS (p=0.378); 6	NS (p=0.171); 8	NS (p=0.951); 5
10	Powder mix/blend	6	8	5
11	Powder sieve/screen	NS (p=0.383); 6	8	5
12	Pelletize/granulate	NS (p=0.383); 6	8	5
13	Powder packaging/transfer	NS (p=0.186); 6	6	5
14	Press set-up	NS (p=0.354); 5	6	5
15	Press	Significant TT[c]	NS (p=0.891); 6	5
16	Shape	Significant TT	NS (p=0.302); 7	5
17	Extrude	6	7	5[a]
18	Cold isostatic press/slug form	NS (p=0.053); 6	7	5
19	Furnace set-up	6	8	4

[a]Exposure interval assigned by professional judgment due to lack of available IH measurements and/or high censoring.
[b]Results given as "NS" (not significant) at $\alpha = 0.05$ with corresponding p-value and resulting exposure assignment.
[c]TT=time trend; $p<0.05$.

TABLE II (continued)

TIME TREND TESTING AND EXPOSURE INTERVALS BY JOB CLASS

Job Class Number	Job Class Group	Co Exposure Interval	W Exposure Interval	Ni Exposure Interval
	General Production Operations			
20	Furnace	Significant TT[c]	8	4
21	Computer numerical control operation	Significant TT	6	4
22	Hone/polish/lap	4	6	4
23	Grind	Significant TT	NS (p=0.593); 6[b]	4
24	Slow moving operations	4	7	4
25	Electro-discharge machining	4	7[a]	4[a]
26	Blast	4	7[a]	4[a]
27	Coat	3	4	3[a]
	Tungsten Carbide Powder Production Operations			
28-30	Powder milling processes	Significant TT	8	5
31	Spray dry	NS (p=0.065); 6	NS (p=0.157); 8	5
32	Mill and spray dry	NS (p=0.084); 7	8	5
33	Ammonium-paratungstate process	3[a]	8[a]	3[a]
34	Thermit process	4	8	6
52	WC powder production unspecified	6[a]	7[a]	5[a]
	Additional Operations			
35	Weld	4	4[a]	4
36	Braze	4	4[a]	3
37; 65	Rapid omni-directional compaction; Foundry	4	4	5
39	Powder room operations	Significant TT	8	6
40;41;63	Ceramic processes	3[a]	4[a]	3[a]

[a]Exposure interval assigned by professional judgment due to lack of available IH measurements and/or high censoring.
[b]Results given as "NS" (not significant) at $\alpha = 0.05$ with corresponding p-value and resulting exposure assignment.
[c]TT=time trend; $p<0.05$.

TABLE II (continued)

TIME TREND TESTING AND EXPOSURE INTERVALS BY JOB CLASS

Job Class Number	**Job Class Group**	**Co Exposure Interval**	**W Exposure Interval**	**Ni Exposure Interval**
	Additional Operations			
42	Dry grind	5	6	4
43	Recycling	NS (p=0.252); 7[b]	8	5
44	Mechanical production	4	4[a]	4
45	Graphite service	6	8[a]	4[a]
46	Heavy metal powder production	Significant TT[c]	NS (p=0.690); 7	5
47	Medical engineering	4[a]	4[a]	4[a]
50	Press/form/sinter	5	6	6
53	W production	3[a]	8[a]	3[a]
55	WC parts production unspecified	5	6	4
56-61	Rolls processes (combined)	6	7	6
62	Hydrogen gas production	3[a]	4[a]	3[a]
64	WC powder/parts production unspecified	5	6[a]	5[a]
66	Tube milling	4	7	4[a]
	Other			
75	Blue collar worker[d]	5[a]	6[a]	5[a]
38, 48-49, 85	Out of plant[e]	0	0	0
	Number of classes with time trend possible	19	6	1
	Number of classes with significant time trend	8	0	0

[a]Exposure interval assigned by professional judgment due to lack of available IH measurements and/or high censoring.
[b]Results given as "NS" (not significant) at $\alpha = 0.05$ with corresponding p-value and resulting exposure assignment.
[c]TT=time trend; $p<0.05$.
[d]No further job classification possible; Germany only.
[e]Includes mine, metals (white collar), metals (blue collar), and leave/time spent out of plant.

there were 19 job classes able to be tested for trends for Co, 6 classes for W, and only 1 for Ni. Eight Co classes had significant time trends. Exposure intervals for job classes with significant Co time trends are shown in Table III; the range of years at each interval is given.

There were limited measurements available for some job class and agent combinations. In these cases, job classes were combined for the exposure analyses. For example, measurements for job classes 11 (Powder Sieve) and 12 (Pelletize) were combined for all agent exposure analyses, whereas measurements for job classes 19 (Furnace Set-up) and 20 (Furnace) were combined for W and Ni exposure analyses only. Exposure intervals were assigned for job classes lacking sufficient IH measurements to analyze via CDA and for those with limited measurements combined with high censoring. These assigned exposure intervals are noted in Tables XI – XIII, Appendices M – O, and in Table II.

4.2 Exposure Estimate Sensitivity

Table IV summarizes the results of the four conditions tested for four Co job classes. The exposure intervals were not sensitive to the corrections up to a factor of 5.0, a fairly extreme correction factor, and only one job class tested was affected at that level. These results indicate that any adjustments applied for inhalable versus total aerosol or CFC versus OFC would not have had a marked effect on the exposure intervals generated.

4.3 Country-Specific Exposure Adjustments

Based upon information from the Austrian researchers, it was learned that Ni was only used through 2005 at their one study plant. A separate JEM for Austrian Ni exposures was made

TABLE III

EXPOSURE INTERVALS FOR SIGNIFICANT COBALT TIME TRENDS BY JOB CLASS

Exposure Interval	Interval Width (mg/m^3)	Interval Midpoint[a]	Press (JC[b] 15)	Shape (JC 16)	Furnace (JC 20)	CNC (JC 21)	Grind (JC 23)	Powder milling (JC 28-30)	Powder room (JC 39)	Heavy metal powder (JC 46)
0	0									
1	< 0.0001									
2	0.0001 - < 0.0005	0.0003								
3	0.0005 - < 0.001	0.00075								
4	0.001 - < 0.005	0.003	2010-2014		2008-2014	2005-2014	2002-2014			
5	0.005 - < 0.01	0.0075	2003-2009	2007-2014	1999-2007	1992-2004	1984-2001			2008-2014
6	0.01 - < 0.05	0.03	1952-2002	1952-2006	1952-1998	1952-1991	1952-1983	1989-2014	2006-2014	1983-2007
7	0.05 - < 0.1	0.075						1952-1988	2000-2005	1952-1982
8	0.1 - < 0.5	0.3							1952-1999	
9	≥ 0.5									

[a]Interval midpoint is the numerical value used in the job exposure matrix.

[b]Job class.

TABLE IV

SENSITIVITY OF PERSONAL COBALT MEASUREMENTS TO INHALABLE AND OPEN-FACE CASSETE CORRECTION FACTORS

Job Class Number	Job Class Group	N	Percent Censored (%)	N (Inhalable)	Percent Inhalable Censored (%)	N (OFC[a])	Percent OFC Censored (%)	Median	Exposure Interval
5	IE: Material handlers, shipping clerks	34	9	5	0	0	N/A	0.00321	4
10	Powder mix/blend	35	0	2	0	3	0	0.02855	6
17	Extrude	35	0	14	0	0	N/A	0.00968	5
27	Coat	33	30	5	80	19	0	0.00048	2
Job Class Number	**Job Class Group**	**Median (1.5 CF[b])**	**Exposure Interval**	**Median (3.0 CF)**	**Exposure Interval**	**Median (3.0 CF and 30% OFC[c])**	**Exposure Interval**	**Median (5.0 CF)**	**Exposure Interval**
5	IE: Material handlers, shipping clerks	0.00303	4	0.00274	4	N/A	N/A	0.00258	4
10	Powder mix/blend	0.02789	6	0.02681	6	0.026	6	0.02604	6
17	Extrude	0.00814	5	0.00605	5	N/A	N/A	0.00486	4
27	Coat	0.00047	2	0.00045	2	0.00032	2	0.00041	2

[a]Open-face cassette.

[b]Correction factor.

[c]Inhalable correction factor applied in conjunction with 30.0 percent reduction to OFC measurements.

and provided to UPitt that set exposures to zero for 2006 onward; for 2005 and prior, the same Ni estimates presented here were used. Adjustments to the JEM were also made for the three Swedish study plants based on process information they gathered. For one Swedish plant Ni exposures spanned the years 1965 – 2014, and for the other two plants Ni exposures spanned the years 1970 – 2014. For all years of exposure, the same Ni estimates presented here were used.

4.4 Task-Based Exposure Estimates

The four tasks performed by job class 4, Trades, were examined in the same manner as the overall job classes. Regression showed that there were no significant Co time trends for cleaning task measurements (n = 49; p = 0.827), for maintenance task measurements (n = 103; p = 0.796), or for warehouse task measurements (n = 45; p = 0.926); there were not enough tooling task measurements (n = 31) to test for the presence of a time trend. The Co task medians were therefore calculated using all measurements according to the MLE CDA method described (see Section 3.1.4). The resulting Co medians (cleaning = 0.0098 mg/m^3; maintenance = 0.0074 mg/m^3; tooling = 0.0023 mg/m^3; warehouse = 0.011 mg/m^3) were then summed and divided by 4 to yield a job class median of 0.0077 mg/m^3. As shown in Table IX, this level of Co exposure would yield an exposure interval of 5 (0.005 - < 0.01 mg/m^3). The same exposure interval for job class 4, Trades, was obtained when tasks were not considered, and there was no significant time trend for the class (n = 228, p = 0.680, median = 0.0073 mg/m^3).

4.5 Qualitative Factor Assessment

Full results from the 10 qualitative factor ANOVA analyses are shown in Appendix P. All factors were significant according to their p-values (all < 0.0001). Because the analyses were performed to determine which factors might exert an influence on measured concentration, the R^2 values (which indicate how much variation in concentration is attributed to the factors) were more informative. The R^2 values are presented and ranked in Table V.

TABLE V

QUALITATIVE FACTOR ANOVA SUMMARY

Factor	**Levels**	**R^2 Percent (%)**	**Rank**
Threshold limit value (TLV) time period	6	23.26	1
Plant	21	22.1	2
Plant type	3	10.98	3
Major job class category	3	10.76	4
Production phase	3	9.3	5
Country	5	2.74	6
Measurement analysis period	3	2.47	7
Age of facility	2	1.47	8
Company	3	1.2	9
Particulate fraction	2	0.31	10

5. DISCUSSION

5.1 Reported Particle Sizes

While there was limited particle size data available for this project, there have been several studies in the hardmetal industry that reported this type of information. Koponen et al. (1981) collected total aerosol of bench grinder operators during sharpening of hardmetal pieces using a silicon carbide wheel. Total personal aerosol concentrations ranged from 5.0 – 9.0 mg/m^3. The fraction of particles with aerodynamic diameter < 7.0 μm, as determined by electron microscopy, was approximately 60.0%. Although the actual particle sizes were not reported, area measurements of total aerosol collected by Koponen et al. (1982) during grinding, forming, pressing, and mixing operations and examined by electron microscopy were "of respirable size" (Koponen et al., 1982, p. 651).

Kusaka et al. (1986) reported that area sample particles < 7.0 μm, collected with an Andersen size-selective sampler in a shaping room, represented 75% of the total aerosol generated during shaping operations. Diameters of WCCo powder particles analyzed by scanning electron microscope showed WC particles less than 5.0 μm and Co particles 2.0 – 3.0 μm; analysis of dust from a grinding machine showed even smaller particles (sizes not reported) (Yamada et al., 1987). The mass median diameter of aerosol collected from area samples (n=6) during hardmetal grinding was 2.8 μm, with the respirable fraction comprising 66.0% of total aerosol (Kusaka et al., 1992). Particle sizing performed with a laser sizer showed the mean diameter of milled powder was 2.3 μm and that 79.1% of particles were less than 8.0 μm; mean diameter during shaping and drilling was 1.5 μm (Scansetti et al., 1998).

Stefaniak et al. (2007) characterized size distributions and physiochemical properties of aerosols generated during hardmetal production processes. Total aerosol and cobalt were examined using a 10-stage impactor. Eleven area measurements were taken at approximately breathing-zone height across six work areas (grinding, pressing, screening, spray drying, powder mixing, and scrap reclamation). Mass median aerodynamic diameters for the 11 total aerosol measurements differed across the six work areas and ranged from 2.0 μm (dry grinding) up to > 18.0 μm (ball milling during scrap reclamation); all other areas were 15.0 μm or less. Respirable masses ranged from 9.0 (ball milling during scrap reclamation) – 56.0 % (pressing). Mass median aerodynamic diameters for the 11 Co-containing measurements taken across the six work areas ranged from 6.0 μm (dry grinding) to > 18.0 μm (pressing and crushing and ball milling during scrap reclamation); all other areas were 17.0 μm or less. Respirable masses ranged from 7.0 (ball milling during scrap reclamation) – 37.0% (dry grinding).

Stefaniak et al. (2009) characterized total aerosol, Co, and W concentrations and particle size distributions. Personal measurements were taken across 21 work areas with 8-stage impactors (n = 108). All mass median aerodynamic diameters from the 8-stage impactor measurements for Co and W were less than 19.0 μm. Mass median aerodynamic diameters for Co ranged from 8.6 μm (maintenance) – 18.4 μm (scrap reclamation) and from 8.9 μm (maintenance) – 18.2 μm (scrap reclamation) for W.

While two studies found particle sizes approaching 20.0 μm for some operations (Stefaniak et al., 2009; Stefaniak et al., 2007), other studies (Scansetti et al., 1998; Kusaka et al., 1992; Kusaka et al., 1986; Koponen et al, 1982; Koponen et al., 1981) and the majority of the operations measured by Stefaniak et al. (2009) and Stefaniak et al. (2007) indicated that the particle sizes generated during hardmetal operations are generally small (i.e., well below 20.0 μm). These studies agree with the particle sizes given by Lassner and Schubert (1999, p. 324, p. 344) and determined by the particle size data available in this study.

For operations where particle sizes approach 20.0 μm (e.g., scrap reclamation), an equal relationship (i.e., 1:1) may not exist between total aerosol and the inhalable fraction. However, because differences between inhalable samplers and 37 mm CFCs are most pronounced for particle sizes greater than 20.0 μm (Buchan et al, 1986), the particle sizes encountered in the majority of hardmetal operations are relatively small, and the exposure interval analyses performed here are insensitive to correction factors applied to individual IH measurements, the determination not to apply corrections for total aerosol/inhalable fraction measurements or CFC/OFC measurements in this study is supported.

5.2 Reported Hardmetal Exposures

The exposure intervals generated for this study are based on IH measurements from the hardmetal study plants and are quantitative in relation to one another; each interval is one-half order of magnitude different from the intervals above and below. Because the intervals are quantitative, they may be compared generally with other published exposure values and limits. With the exception of the lower geometric means of five Co and two W job classes reported in 2016 for measurements recently performed (Klasson et al., 2016), the Co, W, and Ni exposure intervals assigned to cohort members here are similar to or lower than other published values from the hardmetal industry.

Breathing zone total aerosol Co samples were taken by OSHA in 1981 at a hardmetal plant (Auchincloss et al., 1992). The measurements ranged from 0.01 – 0.1 mg/m^3 for lathe room machinists; an inspector in the furnace room had an exposure of 0.014 mg/m^3. Personal total aerosol measurements (n=120) taken at a hardmetal plant for a 1983 study on the relationship between Co air concentrations and bronchopulmonary disease reported arithmetic Co means of 0.03 mg/m^3 for sintering, 0.07 mg/m^3 for wet grinding, 0.19 $mg/m^3$for shaping, 0.56 mg/m^3 for powder handling, 0.66 $mg/m^3$for pressing, and 1.29 mg/m^3 for dry grinding with diamond wheels (Kusaka et al., 1983).

A 1985 study by Ichikawa et al. measured Co levels in blood, urine, and air samples at a hardmetal plant to determine the relationship of biological indices with exposure levels (Ichikawa et al., 1985). Mean Co concentrations for the full-shift personal total aerosol measurements (n=175) ranged from 0.028 mg/m^3 for sintering to 0.367 mg/m^3 for rubber press operations. Mean Co concentrations for operations with more than one group measured ranged from 0.044 – 0.092 mg/m^3 for wet grinding and 0.033 – 0.05 mg/m^3 for shaping. The remaining operations measured had mean Co concentrations of 0.317 mg/m^3 for "workers using respirators" (tasks not defined), 0.186 mg/m^3 for powder handling, and 0.056 mg/m^3 for automatic pressing (Ichikawa et al., 1985, p. 271).

Twenty-six short-term (45 – 60 min) personal total aerosol measurements were taken at one plant for a study on the relationship between Co air and urinary concentrations in the hardmetal industry (Scansetti et al., 1985). Two of the 26 measurements exceeded the 1985 TLV of 0.1 mg/m^3 and 10 exceeded the 1985 recommended TLV change standard of 0.05 mg/m^3. All of the 12 measurements over the two TLV values were taken during forming and hand pressing operations.

An IH study conducted in 1986 at a hardmetal plant reported mean arithmetic total aerosol Co concentrations ranging from 0.003 mg/m^3 for blasting operations (n=5) to 1.29 mg/m^3 for dry grinding (n=2), though it was noted that one worker had an extremely high measurement which decreased after local exhaust ventilation was installed (Kusaka et al., 1986). Other Co means reported were 0.688 mg/m^3 for powder operations, 0.085 mg/m^3 for machine pressing, 0.473 mg/m^3 for rubber pressing, 0.028 mg/m^3 for sintering, 0.126 mg/m^3 for shaping, 0.053 mg/m^3 for wet grinding and 0.004 mg/m^3 for electro-discharge machining. Excluding the dry grinding result, the study showed higher mean Co concentrations for powder and pre-sintering operations and lower means for sintering and finishing operations.

Single personal total aerosol Co measurements taken during four operations at one hardmetal plant were 0.023 mg/m^3 for powder mixing and 0.029 mg/m^3 for cutting; measurements for pressing and grinding/boring were less than the detection limit (Yamada et al., 1987). A cross-sectional study of hardmetal workers examining the relationship between exposure to Co dust and respiratory function obtained personal total aerosol Co measurements at three factories (Meyer-Bisch et al., 1989). By factory (1, 2, and 3), arithmetic mean concentrations for powder operations were 0.117 mg/m^3, 0.272 mg/m^3, and 0.045 mg/m^3; pressing operations were 0.03 mg/m^3, 0.05 mg/m^3, and 0.22 mg/m^3; forming operations yielded 0.16 mg/m^3, 0.11 mg/m^3, and 0.06 mg/m^3; and finishing operations were 0.03 mg/m^3, 0.095 mg/m^3, and 0.21 mg/m^3. Hardmetal grinders (n=133) monitored in 1992 had total aerosol geometric mean concentrations of 0.013 mg/m^3 and 0.001 mg/m^3 for Co and Ni, respectively (Kusaka et al., 1992).

Scansetti et al. investigated the relationship between Co absorption and excretion for three hardmetal plants with high Co levels (Scansetti et al., 1994). Short-term (45 – 60 min) personal total aerosol samples (n=23) were collected in 1987 at one of the three plants. Mean Co concentrations ranged from 0.13 – 0.14 mg/m^3 for shaping or mixing activities to 0.23 mg/m^3 for pressing. Warehouse, grinding, and furnace operations had Co concentrations ≤ 0.05 mg/m^3. Four hardmetal plants with recent LEV improvements were monitored as part of an exposure study of hardmetal and diamond grinding tool production (Sala et al., 1994). The geometric means of personal total Co aerosol measurements were 0.751 mg/m^3 for powder weighing (n=7), 0.303 mg/m^3 for filling and pressing (n=61), 0.248 mg/m^3 for sintering (n=26), 0.039 mg/m^3 for sharpening and grinding (n=28), and 0.205 mg/m^3 for polishing (n=10).

Kumagai et al. (1996) updated a previously monitored hardmetal plant in Japan (Kusaka et al., 1986; Kusaka et al., 1992) using additional measurements and determining exposures for nine job groups. The personal total aerosol Co geometric means ranged from 0.002 mg/m3 for blasting (n=7) and electron discharge machining (n=18) to 0.233 mg/m^3 for rubber press operations (n=26).

Some hardmetal studies stated exposures but did not specify specific tasks performed. Lison et al. (1994) reported personal (n=10) total aerosol Co geometric mean concentrations of 0.009 and .019 mg/m^3 for two days of sampling. Personal total aerosol measurements for Co and

Ni were collected at one hardmetal plant using equal amounts of both as binder material to study Ni exposures and the effect of Ni on the uptake of Co, as determined by urine samples (Scansetti et al., 1998); mean personal measurement concentrations ranged from 0.004 – 0.247 mg/m^3 for Ni (n=20) and from 0.005 – 0.092 mg/m^3 for Co (n=20). A biological monitoring study analyzing Co in urine samples obtained personal total Co aerosol measurements (n=3) ranging from 0.079 – 0.13 mg/m^3 with a mean of 0.1 mg/m^3 (Torra et al., 2005).

A 2007 study characterized size distributions and physiochemical properties of aerosols generated during hardmetal production processes at one company (Stefaniak et al., 2007). Eleven area samples were taken at approximately breathing height across six process areas using a 10-stage impactor. Cobalt concentrations ranged from 0.001 mg/m^3 for dry grinding (n=1) to 0.192 mg/m^3 for scrap loading during scrap reclamation (n=1). A 2009 study at one hardmetal company with three facilities within a 50.0 km radius characterized total aerosol, Co, and W concentrations and particle size distributions (Stefaniak et al., 2009). Geometric means for personal total Co aerosol ranged from 0.0012 mg/m^3 for powder laboratory operations (n=18) to 0.126 mg/m^3 for powder mixing (n=20). For personal total W aerosol, geometric means ranged from 0.0109 mg/m^3 for sandblasting (n=8) to 0.432 mg/m^3 for powder screening (n=7).

Klasson et al. (2016) collected total aerosol and total, Co, and W inhalable fraction measurements at one hardmetal plant for use in risk assessment and examination of dose-response as part of a medical investigation. Personal inhalable Co concentrations ranged from 0.000028 mg/m^3 (inspection; n=4) to 0.0056 mg/m^3 (powder production; n=9). Geometric means for inhalable Co ranged from 0.00006 mg/m^3 (inspection; n=4) to 0.0043 mg/m^3 (powder production; n=9); the overall geometric mean for all departments measured was 0.00068 mg/m^3. Similar to Co, personal inhalable W concentrations were highest in powder production (0.570 mg/m^3; n=9) and lowest in inspection (0.00027 mg/m^3). Geometric means for inhalable W were also highest in powder production (0.05 mg/m^3) and lowest in inspection by two orders of magnitude (0.0005 mg/m^3), and the overall geometric mean for all departments was = 0.0056 mg/m^3.

The reported Co exposures experienced by hardmetal workers described above indicate a decline over time, and, though differing among process-specific exposures, were generally higher for pre-sintering operations as opposed to sintering and post-sintering operations, as was observed here. There were too few hardmetal studies that characterized W or Ni to determine whether these exposures decreased over time; however, observation of the general decline of exposures over time has been made in other industries (Symanski et al., 2000; Symanski et al., 1998; Symanski et al, 1996). In this study there were only eight significant decreasing time trends detected, all for Co. An assumption could have been made that hardmetal exposures overall have declined since 1952 due to various implemented risk management measures (e.g., ventilation improvements, process enclosures, automation, etc.). However, such measures had various implementation times and depended upon the specific plant, process, and even machine; control information was seldom contained with the IH measurements (< 20% had ventilation information). Aside from PPE use, exposure reductions due to ventilation improvements and machine upgrades would have been generally reflected in the values of the personal IH measurements collected over the years. Therefore, no formal corrections were made for risk management measures. Lack of time trend detection does not imply that these measures had no effect on exposures, especially for individual workers. With the available data, however, statistically significant decreases over time for most job classes were not observed. The limited number of IH measurements available for some agent and job class combinations may have contributed to the number of significant trends detected.

In 2016 ACGIH adopted a hardmetal TLV with a recommended level of 0.005 mg/m^3 (as Co, thoracic fraction) for WC and hardmetals containing Co (ACGIH, 2016). Minimal differences in collection efficiency among inhalable and thoracic fractions and total aerosol would be expected due to the small particle sizes observed in the hardmetal industry (ACGIH, 2016, p. 80). However, the available data were total aerosol and inhalable fraction measurements and the TLV is based on Co content, therefore the exposure estimates generated were compared to the Co, W, and Ni TLVs.

The exposure interval estimates generated for Co were above the current ACGIH TWA TLV of 0.02 mg/m^3 (total aerosol, elemental and inorganic compounds) (ACGIH, 2016) for 13 job classes without time trends (see Table II). Two classes, scrap recycling and milling and drying, had interval 7 exposures (0.05 - < 0.1 mg/m^3), and the other 11 classes (mainly powder production and pre-sintering operations) had interval 6 exposures (0.01 - < 0.05 mg/m^3). The remaining job classes in Table II had Co exposures < 0.01 mg/m^3 (interval 5 or lower). For the eight job classes with significant time trends, all classes at some point experienced exposure intervals above the current Co TLV during the 1952 – 2014 study period (see Table III). No job classes in Table II were above the current 5.0 mg/m^3 TWA TLV (ACGIH, 2016) for metal and insoluble W compounds (total aerosol); the highest W exposures were < 0.5 mg/m^3. The current

1.5 mg/m^3 TWA TLV for metal and elemental Ni (ACGIH, 2016) is based on the inhalable fraction only. The highest Ni exposures, based on total and inhalable measurements combined, were from 0.01 - < 0.05 mg/m^3. Even assuming all Ni particles in the exposure interval concentrations were inhalable, there are no job classes above the TLV (see Table II). None of the job classes exceeded the lower European Ni limit of 0.5 mg/m^3 based on total aerosol or, even assuming all particles were inhalable, the United Kingdom (Great Britain) limit of 0.5 mg/m^3 (see Table VI, Appendix B).

5.3 Agent Collinearity

All agents examined (Co, W, and Ni) are collinear, i.e., present to some degree simultaneously. According to Loomis et al. (1999, p. 88), "Correlations between possible indices of exposure can be examined and only those that provide independent information need be considered." While Co, W, and Ni are collinear, they are present in varying amounts depending on the hardmetal formulation and therefore provided independent information on the specific agents encountered in the workplace.

If agents are true heterogeneous mixtures, like diesel exhaust, Kauppinen (1994) recommended selecting a marker to be used as a surrogate measure. Although total aerosol is not a true heterogeneous mixture, WC and Co in combination acquire properties different from their components and have been shown to be more mutagenic together than alone (IARC, 2006). While W and Co can be analyzed individually, WC with Co (as a bound matrix unit after sintering) cannot be separated out as WCCo by existing analytical methods. Therefore, while it would be ideal because of the potential for increased toxicity to evaluate WCCo, it is not currently possible.

While exposure indicators are often selected based on available measurements, exposure misclassification may occur with the use of nonspecific indicators of exposure (Friesen et al, 2007). In a study of sawmill workers, specific indicators (wood dust, tetrachlorophenol) were more strongly associated with the health outcomes investigated than were nonspecific indicators (dust, chlorophenols) (Friesen et al., 2007). The effect of agent combination on misclassification and effect "dilution" were also reported previously by Kauppinen (1994, p. 21).

In this study, total aerosol estimates would not have provided further independent information (in addition to that provided by Co, W, and Ni alone) in terms of specificity of the exposure-response analyses conducted by UPitt for the occupational epidemiological study. It would also be difficult, should an association be detected between total aerosol and any mortality outcome, to further tease out causative agents other than Co, W, or Ni or any relevant size fractions given the data available here. Conversely, if any association were found with Co, W, or Ni then this would imply that levels of that agent, and consequently total aerosol exposures, should be reduced. A toxicokinetic investigation might reveal more useful mechanistic information regarding specific etiology of any possibly detected excess mortality outcome than could be determined from an occupational epidemiological study.

5.4 Hierarchical/Interval Approach

There are many ways that one could potentially approach an exposure reconstruction for use in an occupational epidemiological study. Other research teams involved in the overall international study approached their country-specific independent exposure reconstructions in varying ways depending on their available data and study-specific needs. The almost infinite choices of exposure indices and models are ultimately influenced by the investigators' worldviews and beliefs (Loomis et al., 1999). The challenge then becomes, according to Loomis et al. (1999), how to reach "…agreement on how to select good exposure-response models in a given situation, draw reasonable inferences from them, and report the decision process to various audiences, while recognizing that an answer that is universally "best" is unlikely to be found" (p. 86). Given the pooled international data available and the desire to create a qualitative ranking of job classes suitable for inclusion in the US and pooled epidemiological analyses, the technique selected for this project was the hierarchical approach presented in Figure 1.

One objective of an exposure reconstruction is to generate groups that are sufficiently different in order to identify possible dose-responses in the epidemiological analyses. As seen in Table IV, the intervals generated are not sensitive to quite dramatic adjustments to the individual measurements for total versus inhalable aerosols and CFC versus OFC measurement techniques. It is therefore reasonable that additional, smaller adjustments both known (e.g., a 10.0% adjustment for sampling method) and unknown would not have a marked impact on the resulting intervals.

5.5 Qualitative Factors

The aim of the qualitative factor analyses was to detect factors that potentially had an effect on measured concentrations of the agents included in the study (Co, W, and Ni). An important point is that the analyses were not run to determine a predictive regression equation (e.g., a pre-sintered measurement for Co taken in 1985 during a non-powder operation at plant X, which only performs manufacturing operations, is some particular value.) While such an equation could have been easily generated, it was not useful in the context of this study (i.e., the measured concentrations were known) and would be of limited, if any, value to other projects. The factor analysis was also not performed to generate exposure estimates. Rather the idea was to take a "global" look at what factors may exert an influence and should be given consideration, whether incorporated or not, in an exposure reconstruction.

Four of the five highest R^2 values in Table V (plant, plant type, major job class category, and production phase) make sense in the context of this study. While these factors were not specifically included in the exposure estimate calculations, job class was accommodated directly by the job class scheme and production phase and plant type were indirectly accommodated by the job class scheme (i.e., the job classes reflected pre- and post- sintering processes and shared and plant-specific processes).

The highest R^2 value was for TLV time period (23.26%). Its effect on measured concentration was demonstrated in a study analyzing long-term trends across industries (Symanski et al., 1998). The OELs for the European countries (see Table I, Appendix B) are generated in various ways and may not be similar to the procedures used by US groups.

Therefore, the TLV time period finding may not be as relevant for all countries outside of the US. However, the analysis examined IH measurements from all countries and the effect was found across the whole dataset. This finding, which was based upon all agents and job classes in one analysis, does not imply refinements to the time trend analysis performed in this study (which detected few significant trends) would be warranted given the large number of IH measurements available to detect time trends based on specific agent and job class combinations. Consideration of the TLV time period effect may however be useful for reconstructions where there are fewer or no measurements available.

Given the insensitivity of the IH measurements in this study to correction factors, inclusion of TLV effects (i.e., correcting by 23%) would not have had an impact on the generated exposure estimates. Nevertheless, it is an interesting finding that highlights the influence recommended standards can exert on measured concentrations.

Particulate fraction had the lowest R^2 (0.31%), further supporting the use of uncorrected total aerosol and inhalable fraction measurements to generate the exposure estimates. Country, measurement analysis period, age of facility, and company had R^2 values less than 3.0%, indicating that they did not strongly influence measured concentration in this study. Thus the decision to combine measurements from all companies and countries and not to correct for analysis method in the exposure estimate analyses was supported. Given the similarity of the analytical methods and processes across countries and companies this is not a surprising result. It is possible that these lower-ranking factors may have more observed influence in another study of a more disparate industry or of multiple industries.

The qualitative factor analysis highlighted the importance of considering, describing, and addressing such parameters in an exposure reconstruction whether or not they are ultimately included in any formal way. Exposure reconstruction efforts often select time periods or intervals to examine based upon available data or to make ensuing epidemiological analyses more straightforward. The finding (similar to Symanski et al. (1998)) that TLV time periods were found to exert the most influence of the factors considered on measured concentrations could possibly impact the way a reconstruction is approached (e.g., selecting time intervals based upon regulatory changes as opposed to available measurements).

5.6 Study Limitations

Country-specific investigators assigned job class to the work history lines of their countries' workers. There was the potential for misclassification of workers by assigning the job title/worker to the wrong class given the information present, and it is also possible that investigators from different countries could have assigned the same work history line differently. Because of language and privacy issues it was not possible for all work history lines to be assigned by a common group or person, therefore an attempt was made to reduce job misclassification by having all investigators use common, well-defined job classes during the process.

As is common in many retrospective exposure reconstructions, the study was limited by the extant data, which did not cover all time periods for all operations. In order to improve the coverage, IH measurements from all 12 US and nine European plants were pooled to generate exposure estimates that applied to all facilities. Country-specific investigators assigned job class to the IH measurements, which could have led to potential misclassification in cases where there may not have been enough relevant information to properly classify the measurement. Investigators used all information available and followed up with plant personnel when necessary in order to make the most informed assignment possible.

While the potential for plant-level exposure variations existed due to factors such as LEV and PPE use, this type of information was absent from the majority (over 80%) of the personal IH measurements thus precluding its consideration in the exposure reconstruction.

Due to the scarcity of IH measurements for certain operations and years, exposure intervals were assigned by professional judgment for some job classes as indicated in Tables XI – XIII, Appendices M – O. In these cases, knowledge of the process and information from plant personnel were used to help make the most reasonable assignment. To mitigate bias during the entire exposure reconstruction process, UIC had no knowledge of the specific jobs held by any individual US or European worker or, if deceased, their cause of death. Despite the hierarchical approach used to avoid highly censored datasets for generating the exposure estimates, some job classes with limited measurements remained more than 50.0% censored. While it has been recommended not to use MLE CDA for > 50.0% censored datasets as a general rule of thumb (EPA, 2006, pp. 130 - 136), simulations have shown satisfactory results using this approach on data similar to the type found in the majority of this study's job classes (i.e., lognormally distributed data, sample sizes ≥ 5, censoring levels 0 – 80.0%) (Hewett and Ganser, 2007).

It was not possible to determine Co, W, and Ni exposures by particle size fraction, which can differ by operation (Stefaniak et al, 2009; Stefaniak et al., 2007; Scansetti et al., 1998), given the available IH measurements. Because of the varying nature of the work performed in the hardmetal industry (e.g., different powder formulations and production schedules), ideally repeated size distribution measurements or side-by side sampling with different devices made at all study sites and processes under consideration would be obtained in order to determine any necessary process-specific correction factors. Applying a universal correction factor to change from one fraction to another, such as that suggested for conversion of total MWF aerosol to the thoracic fraction (Stefaniak et al., 2009; Verma et al., 2006; NIOSH, 1998, p. 147), to the individual measurements in this study would not have had any substantial effect on their resulting rank order as demonstrated by the application of multiple conversion factors.

There was some uncertainty surrounding Ni usage at the US and European study plants. However, because the exposure estimates were based on available IH measurements (i.e., Ni was present at some level at the plant where the measurement was taken) and process details from knowledgeable plant personnel, the likelihood that Ni exposures were attributed to plants or years where no Ni was present is minimal.

It was not possible to generate independent exposure estimates for carbon black, WC, or WCCo because there are no analytical methods specific to these combined agents (i.e., usually reported as total aerosol) and therefore no IH measurements available. Because of the collinearity of the agents considered for the JEMs (i.e., they are all present at some level for all job classes), it might not be possible to separate out the effects of Co, W, or Ni exposure alone should an association with a health effect be detected in the epidemiological analyses, although this is an issue common to hardmetal industry mortality studies.

Task-specific details (i.e., tasks performed and task times) were lacking from the IH measurements, which precluded a broader analysis of the potential effect of task on generated exposure intervals using additional job classes. Where details on tasks performed were available and able to be analyzed for one job class, no difference was found between the Co exposure medians generated with and without task consideration. A change in exposure intervals with tasks considered may have indicated that the assumption of uniform task distribution was incorrect; given the lack of information on task times, and the effect on ranking that errors in task time estimates may yield (Burstyn, 2009), this was the most logical assumption. These results should not be interpreted as task not having a potential influence on hardmetal exposures, as shown in studies of other industries (Hansen and Whitehead, 1988; Eduard and Bakke, 1999; Burstyn, 2009), but rather that such an effect could not be detected using the available data in the limited analysis performed here.

One limitation of the qualitative analysis was the inability to identify all relevant factors. This could be either because the factors were not considered (i.e., unknown) or because they could not be assessed from the data (e.g., PPE or LEV use).

5.7 Study Strengths

This study provided, to the author’s knowledge, one of the largest IH datasets used for exposure reconstruction in the hardmetal industry. The large number of IH measurements allowed generation of exposure estimates for background and intermediate job classes (see Tables XI – XIII, Appendices M – O), which are often not adequately represented in IH measurements available for reconstruction, and also covered a large span of the time period to be reconstructed (see Table X, Appendix L). The amount and time range of measurements collected from 21 plants, five countries, and three companies allowed a quantitative assessment of three agents to be conducted, two of which (W and Ni) were not considered separately in prior hardmetal cohort mortality studies (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990).

"Blinding techniques" (i.e., exposure assignment without knowledge of health outcomes) have been noted as one of the best ways to mitigate differential misclassification, in which misclassification is dependent on the health outcome of interest (Kauppinen, 1994, p. 27). These techniques cannot guarantee no misclassification will occur, or that it will be limited to nondifferential types (Flegal et al., 1991; Wacholder et al., 1991). The "firewall" between UIC and UPitt regarding mortality outcomes among the workforce, however, along with the use of exposure intervals as opposed to collapsed or dichotomous categories, helped reduce the likelihood of differential misclassification in work history assignments and in generating the exposure estimates, especially in the cases where exposure interval assignments for a job class were made via professional judgment.

Access to particle size-specific data from one European study site, while limited, helped aid the investigation into whether or not to combine total aerosol and inhalable measurements in the exposure estimate analyses. Because the exposure interval estimates are insensitive to rather large known possible adjustments, the likelihood of other smaller known (e.g., different analytical methods used, such as AA or ICP) or even unknown differences is unlikely to have a pronounced effect on the estimates. Additionally, the exposure reconstruction generated job classes and exposure groups that provided the necessary level of differentiation for epidemiological analyses of mortality outcomes.

An analysis of qualitative factors that potentially influenced measured concentration was performed, and further supported the approach used in this study to generate the exposure estimates (i.e., no corrections for the IH measurements used in the exposure analyses).

This study incorporated the majority of the steps outlined in the Sahmel et al. (2010) recommended framework for a quality exposure reconstruction appropriate for its purpose. The study did not incorporate probabilistic methods (step 5 of the framework) to evaluate parameter variability; however, given the large number of IH measurements used and limited professional judgments made this step would not have likely yielded much, if any, improvement in the estimates. The lack of validations (step 7 of the framework) performed for reconstructions and attendant assumptions of reliability and accuracy has been noted previously (Esmen, 1991); validation is often difficult because past exposures are unknown (Kauppinen, 1994). While there was no formal validation step, in this study the large number and high quality of measurements available, minimal modeling performed for generating the exposure estimates, as well as the agreement of the estimates with published data from the industry (see Section 5.2) all provide greater confidence in the results.

An important consideration in occupational epidemiological studies is that if exposure is underestimated then the health outcome of interest will be overestimated (i.e., a very low exposure causes an observed health effect), and if exposure is overestimated the outcome will be underestimated (i.e., a very high exposure causes an observed effect) (Ulfvarson, 1983). This phenomenon has implications for both regulatory/advising bodies and industry. An OEL set too high may result in additional adverse health outcomes and one set too low would misrepresent the true dose-response relationship. Within industry exposures may be over-controlled for a low OEL, leading to unnecessary costs, or under-controlled for a high OEL, leading to additional illness and potential litigation. Because of these important implications the hierarchical and interval approaches, which generated quantitative estimates while incorporating inherent variability, were used in the exposure reconstruction performed for this study.

6. CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

The quantitative exposure estimates generated for Co, W, and Ni over the time period 1952 – 2014 were similar to or less than other published values over the same period. Thirteen job classes without time trends were over the current ACGIH TLV for Co (0.02 mg/m^2), and all eight job classes with significant Co time trends exceeded the TLV at some point during the study period; no W or Ni exposures exceeded the current TLVs (ACGIH, 2016). The exposure estimates alone however do not provide an indication of whether workers exposed at these levels have an increased risk of mortality, and there are differences among advisory bodies regarding the carcinogenicity of Co, Ni, and WC/hardmetal powders (ACGIH, 2016; NTP, 2016; IARC, 2012; IARC, 2016). The current occupational epidemiological investigation, which incorporates the exposure estimates from this study, will help provide further answers to the important concern of increased mortality due to lung cancer in the hardmetal industry.

An analysis of exposure estimate sensitivity to measurement correction factors showed that corrections up to a factor of five, a fairly extreme correction, would not have resulted in interval changes. This indicated that other smaller known (e.g., analytical methods) and unknown factors were unlikely to exert much influence on the estimates generated. Exposure estimates were also insensitive to task difference within the one job class examined. Only one job class was analyzed for task sensitivity due to available measurement details. The results do not imply that task has no effect on exposures, but rather that it was not demonstrated in the analysis conducted for this study.

Qualitative factor analysis showed that ACGIH TLV time period exerted the most influence on measured concentrations, which is a finding replicated from an earlier study examining such factors (Symanski et al., 1998). Given the insensitivity of the IH measurements to correction factors, accounting for the amount of variation explained by the TLV time period factor (23.2%) would not have impacted the exposure estimates generated. The analysis did however highlight the importance of considering qualitative factor effects on measured concentrations as well as the effects that recommended standards can have on the workplace environment.

Exposure assessments for prior epidemiological studies of the industry used broad classes and limited data and did not include W or Ni (Wild et al., 2000; Moulin et al., 1998; Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990). The amount and quality of IH measurements available for use in this study, the hierarchical approach employed, the number of job classes for which estimates were obtained, the insensitivity of the estimates to measurement correction factors and tasks, and the consideration of qualitative factor influence helped improve upon these prior assessments. The results obtained in this study provide the necessary job and exposure differentiation required for the current occupational epidemiological mortality study of US and European hardmetal workers being conducted by UPitt.

6.2 Recommendations

For IH practice in general, which for larger companies is often outsourced to consulting groups, thorough information for each measurement should be obtained including task and, when possible, task times. Although task differences were not detected here, such information should be captured/detailed when collecting IH measurements to assist with decisions regarding high exposure tasks and controls. Particle size-specific sampling of various operations should be performed not only to comply with the more numerous particle size-specific ACGIH recommendations but also to gather useful information about processes, best control methods, and most likely health effects.

There is no omnibus exposure reconstruction method considered "best." For example, a prior study conducted by Kennedy et al. (2013) had ample, but fewer, IH measurements and a vast array of other supporting documentation (e.g., engineering time studies) available, therefore different approaches were used than those in this study. Regardless of the methods ultimately selected, exposure reconstructions should attempt to incorporate elements of previously recommended frameworks (e.g., such as that presented in Sahmel et al., 2010). It is imperative that reconstructions be very clear on what information was used, what judgments were made, and the limitations of the applied method. Incorporation of probabilistic methods, when appropriate, remains an area for further work in reconstruction. Future studies should also consider the potential impact of qualitative factors, even if they are not ultimately included in the analyses.

No occupational epidemiological study or exposure reconstruction can be performed successfully if there is not cooperation among all involved. To ensure the best study possible, cooperation must be achieved among investigators, funders, corporate/plant management, operators, and other stakeholders. In order to further that cooperation, it is vital that investigators are as clear and transparent as possible throughout the study about their methods, progress, unexpected issues, and timeline. In addition to the stated objectives of an exposure reconstruction/occupational epidemiological investigation, industry may have additional concerns the investigators should be willing to address and answer if feasible (e.g., in this study, exposure levels in pre- versus post-sintering operations and exposures of one particular job class compared to others).

Despite one's best plans for an exposure reconstruction, ultimately the approach used depends on the IH measurements and relevant information available. The availability and quality of resources is often not fully known until the project is well under way. One must be able to adapt methods appropriately in order to generate the most scientifically defensible exposure estimates given the available information. Frequently related issues arise in the course of a project, such as particle characteristics and sampler behavior here, and must be pursued and resolved satisfactorily to ensure a quality study.

CITED LITERATURE

Agency for Toxic Substances and Disease Registry (ATSDR): Toxicological Profile for Tungsten. U.S. Department of Health and Human Services, Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA, 2005.

American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th edn. American Conference of Governmental Industrial Hygienists, Cincinnati, OH, 1991.

American Conference of Governmental Industrial Hygienists (ACGIH). Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists. Cincinnati, OH, 1986 – 2016.

Aizenberg, V., Chloe, K., Grinshpun, S.A., Willeke, K., and Baron, P.A.: Evaluation of personal aerosol samplers challenged with large particles. J. Aerosol Sci. 32:779-793, 2001.

Armstrong, B.G. and Oakes, D.: Effects of approximation in exposure assessments on estimates of exposure-response relationships. . Scand. J. Work Environ. Health 8 (Suppl 1):20-23, 1982.

Auchincloss, J., Abraham, J., Gilbert, R., Lax, M., Hennenberger, P., Heitzman, E., and Peppi, D.: Health hazard of poorly regulated exposure during manufacture of cemented tungsten carbides and cobalt. Br. J. Ind. Med. 49:832-836, 1992.

Baldwin, P.E.J. and Maynard, A.D.: A survey of wind speeds in indoor workplaces. Ann. Occup. Hyg. 42:303-313, 1998.

Baron, P.A.: Factors affecting aerosol sampling. In: NIOSH Manual of Analytical Methods, 4th ed., 3rd supplement, pp. 184-207. Cincinnati, National Institute of Occupational Safety and Health; 2003.

Beaulieu, H.J., Fidino, A.V., Arlington, K.L.B., and Buchan, R.M.: A comparison of aerosol sampling techniques: “open” versus “closed-face” filter cassettes. Am. Ind. Hyg. Assoc. J. 41:758-765, 1980.

Buchan, R.M., Soderholm, S.C., and Tillery, M.I.: Aerosol sampling efficiency of 37 mm filter cassettes. Am. Ind. Hyg. Assoc. J. 47:825-831, 1986.

Burstyn, I.: Measurement error and model specification in determining how duration of tasks affects level of occupational exposure. Ann. Occup. Hyg. 53:265-270, 2009.

Code of Federal Regulations (CFR). Title 29. Part 1910, Occupational Safety and Health Standards.

CITED LITERATURE (continued)

Cohen, A.C.: Truncated and Censored Samples: Theory and Applications. New York, Marcel Dekker, Inc., 1991.

Creely, K.S., Cowie, H., Van Tongeren, M.V., Kromhout, H., Tickner, J., and Cherrie, J.W.: Trends in inhlation exposure-A review of the data in the published scientific literature. Ann. Occup. Hyg. 51:665-678, 2007.

Demange, M., Görner, P., Elcabache, J.M., and Wrobel, R.: Field comparison of 37-mm closed face cassettes and IOM samplers. Appl. Occup. Environ. Hyg. 17:200-208, 2002.

Eduard, W. and Bakke, B.: Experiences with task-based exposure assessment in studies of farmers and tunnel workers. Nor. Epidemiol. 9:65-70, 1999.

Environmental Protection Agency (EPA). *Data Quality Assessment: Statistical Methods for Practitioners.* Environmental Protection Agency Pub. No. QA/G-9S, 2006.

Esmen, N.A., Kennedy, K.J., Hall, T.A., Phillips, M.L., and Marsh, G.M.: Classification of worker exposures. Chem. Biol. Interact. 166:245-253, 2007a.

Esmen, N.A., Hall, T.A., Phillips, M.L., and Marsh, G.M.: Chemical process based reconstruction of exposures for an epidemiological study. I. Theoretical and methodological issues. Chem. Biol. Interact. 166:254-263, 2007b.

Esmen, N.A. and Hall, T.A.: Theoretical investigation of the interrelationship between stationary and personal sampling in exposure estimation. Appl. Occup. Environ. Hyg. 15:114-119, 2000.

Esmen, N.A.: Exposure estimation in four major epidemiologic studies in the acrylonitrile industry. Scand. J. Work Environ. Health 24 (Suppl 2):63-70, 1998.

Esmen, N.A.: Analysis of strategies for reconstructing exposures. Appl. Occup. Environ. Hyg. 6:488-494, 1991.

Esmen, N.A.: Retrospective industrial hygiene surveys. Am. Ind. Hyg. Assoc. J. 40:58-65, 1979.

Esmen, N.A. and Hammad, Y.Y.: Log-normality of environmental sampling data. J. Environ. Sci. Health B. 12:29-41, 1977.

“Air Contaminants, Final Rule.” *Federal Register* 58 (30 June 1993): 35338-35351.

“Air Contaminants, Final Rule.” *Federal Register* 54 (19 January 1989): 2332-2983.

Federal Register 36 (29 May 1971): 10466.

CITED LITERATURE (continued)

Flegal, K.M., Keyl, P.M., and Nieto, F.J: Differential misclassification arising from nondifferential errors in exposure measurement. Am. J. Epidemiol. 134:1233-1244, 1991.

Friesen, M.C., Davies, H.W., Teschke, K., Ostry, A.S., Hertzman, C., and Demers, P.A.: Impact of the specificity of the exposure metric on exposure-response relationships. Epidemiology 18:88-94, 2007.

Gamble, J. and Spirtas, R.: Job classification and utilization of complete work histories in occupational epidemiology. J. Occup. Med. 18:399-402, 1976.

Goldberg, M., Kromhout, H., Guénel, P., Fletcher, A.C., Gérin, M., Glass, D.C., Heederik, D., Kauppinen, T., and Ponti, A.: Job exposure matrices in industry. Int. J. Epidemiol. 22 (Suppl 2):10-15, 1993.

Greife, A.L., Hornung, R.W., Stayner, L.G., and Steenland, K.N.: Development of a model for use in estimating exposure to ethylene oxide in a retrospective cohort mortality study. Scand. J. Work Environ. Health 14 (Suppl 1):29-30, 1988.

Gunter, K.L. and Sutherland, J.W.: An experimental investigation into the effects of process conditions on the mass concentrations of cutting fluid mist in turning. J. Clean. Prod. 7:341-350, 1999.

Haan, D.M., Batzer, S.A., Olson, W.W., and Sutherland, J.W.: An experimental study of cutting fluid effects in drilling. J. Mater. Process Technol. 71:305-313, 1997.

Hallock, M.F., Smith, T.J., Woskie, S.R., and Hammond, S.K.: Estimation of historical exposures to machining fluids in the automotive industry. Am. J. Ind. Med. 26:621-634, 1994.

Hansen, D.J. and Whitehead, L.W.: The influence of task and location on solvent exposures in a printing plant. Am. Ind. Hyg. Assoc. J. 49:259-265, 1988.

Hewett, P. and Ganser, G.H.: A comparison of several methods for analyzing censored data. Ann. Occup. Hyg. 51:611-632, 2007.

Hinds, W.C.: Data analysis. In: Cascade Impactor Sampling and Data Analysis, eds. J.P. Lodge and T.L. Chan, pp. 45-78. Akron, American Industrial Hygiene Association, 1986.

Hogstedt, C. and Alexandersson, R.: Causes and death among hardmetal workers. Arbete och Hälsa 21:1-26, 1990.

CITED LITERATURE (continued)

International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, volume 100C, Arsenic, Metals, Fibres, and Dusts. Lyon, France, IARC, 2012. Accessed January 9, 2017, http://monographs.iarc.fr/ENG/Monographs/vol100C/.

International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, volume 86, Cobalt in Hardmetals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Lyon, France, IARC, 2006.

Ichikawa, Y., Kusaka, Y., and Goto, S.: Biological monitoring of cobalt exposure, based on cobalt concentrations in blood and urine. Int. Arch. Occup. Environ. Health 55:269-276, 1985.

Joint ACGIH-AIHA Task Group on Occupational Exposure Databases. Data elements for occupational exposure databases: Guidelines and recommendations for airborne hazards and noise. Appl. Occup. Environ. Hyg. 11:1294-1311, 1996.

Kauppinen, T. P.: Assessment of exposure in occupational epidemiology. Scand. J. Work Environ. Health 20:19-29, 1994.

Kennedy, K.J., Esmen, N.A., Hancock, R.P., Lacey, S.E., Marsh, G.M., Buchanich, J.M., and Youk, A.O.: Long-term health experience of jet engine manufacturing workers: VII. Occupational exposures. J. Occup.Env. Med. 55:676-689, 2013.

Klasson, M., Bryngelsson, I., Petterson, C., Husby, B., Arvidsson, H., and Westberg, H.: Occupational exposure to cobalt and tungsten in the Swedish hardmetal industry: Air concentrations of particle mass, number, and surface area. Ann. Occup. Hyg. 60:684-699, 2016.

Koponen, M., Gustafsson, T., Kalliomäki, P., Kalliomäki, K., and Moilanen, M.: Grinding dusts of alloyed steel and hardmetal. Ann. Occup. Hyg. 24:191-204, 1981.

Koponen, M., Gustafsson, T., and Kalliomäki, P.: Cobalt in hardmetal manufacturing dusts. Am. Ind. Hyg. Assoc. J. 43:645-651, 1982.

Kumagai, S., Kusaka, Y., and Goto, S.: Cobalt exposure level and variability in the hard metal industry of Japan. Am. Ind. Hyg. Assoc. J. 57:365-369, 1996.

Kusaka, Y., Ichikawa, Y., Sugimoto, K., and Goto, S.: Bronchopulmonary diseases due to hard metal dust. Jpn. J. Ind. Health 25:155-160, 1983.

CITED LITERATURE (continued)

Kusaka, Y., Yokoyama, K., Sera, Y., Yamamoto, S., Sone, S., Kyono, H., Shirakawa, T., and Goto, S. Respiratory disease in hardmetal workers: An occupational hygiene study in a factory. Br. J. Ind. Med. 43:474-485, 1986.

Kusaka, Y., Kumagai, S., Kyono, H., Kohyama, N., and Shirakawa, T. Determination of exposure to cobalt and nickel in the atmosphere in the hard metal industry. Ann. Occup. Hyg. 36:497-507, 1992.

Lasfargues, G., Wild, P., Moulin, J.J., Hammon, B., Rosmorduc, B., Rondeau du Noyer, C., Lavandier, M., and Moline, J.: Lung cancer mortality in a French cohort of hard-metal workers. Am. J. Ind. Med. 26:585-595, 1994.

Lassner, E. and Schubert, W.D.: Tungsten: Properties, Chemistry, Technology of the Element, Alloys, and Chemical Compounds. New York, Plenum Publishers, 1999.

Lison, D., Buchet, J-P., Swennen, B., Molders, J., and Lauwerys, R. Biological monitoring of workers exposed to cobalt metal, salt, oxides, and hard metal dust. Occup. Environ. Med. 51:447-450, 1994.

Loomis, D., Salvan, A., Kromhout, H., and Kriebel, D.: Selecting indices of occupational exposure for epidemiologic studies. Occup. Hyg. 5:73-91, 1999.

Meyer-Bisch, C., Pham, Q., Mur, J., Massin, N., Moulin, J., Teculescu, D., Carton, B., Pierre, F., and Baruthio, F.: Respiratory hazards in hard metal workers: a cross sectional study. Br. J. Ind. Med. 46:302-309, 1989.

"Rules." Michigan Occupational Safety and Health Administration (MIOSHA). Michigan Administrative Code Part 301, Air Contaminants for General Industry, 2013.

Minitab 17 Statistical Software (2010). [Computer software]. State College, PA: Minitab, Inc. (www.minitab.com)

Moulin, J.J., Wild, P., Romazini, S., Lasfargues, G., Peltier, A., Bozec, C., Deguerry, P., Pellet, F., and Perdrix, A.: Lung cancer risk in hard-metal workers. Am. J. Epidemiol. 148:241-248, 1998.

National Institute for Occupational Safety and Health (NIOSH). "Appendix G: 1989 Air Contaminants Update Project – Exposure Limits NOT in Effect." NIOSH Pocket Guide to Chemical Hazards. Last updated March 7, 2016a. Accessed December 9, 2016. https://www.cdc.gov/niosh/npg/nengapdxg.html.

National Institute for Occupational Safety and Health (NIOSH). "Appendix C – Supplementary Exposure Limits." NIOSH Pocket Guide to Chemical Hazards. Last updated March 7, 2016b. Accessed December 9, 2016. http://www.cdc.gov/niosh/npg/nengapdxc.html.

CITED LITERATURE (continued)

National Institute for Occupational Safety and Health (NIOSH). *Criteria for a Recommended Standard: Occupational Exposure to Metalworking Fluids.* Department of Health and Human Services (NIOSH) Pub. No. 98-102, 1998.

National Toxicology Program (NTP). *Report on Carcinogens*, 14th edn. Research Triangle Park, NC, U.S. Department of Health and Human Services, Public Health Service, 2016. Accessed January 9, 2017. http://ntp.niehs.nih.gov/go/roc14/.

Occupational Safety and Health Administration (OSHA). “Permissible Exposure Limits – Annotated Tables.” Occupational Safety and Health Administration. Accessed August 25, 2016. https://www.osha.gov/dsg/annotated-pels/.

Rajan, B., Alesbury, R., Carton, B., Gérin, M., Litske, H., Marquart, H., Olsen, E., Scheffers, T., Stamm, R., and Woldbaek, T.: European proposal for core information for the storage and exchange of workplace exposure measurements on chemical agents. Appl. Occup. Environ. Hyg. 12:31-39, 1997.

Ramachandran, G.: Occupational Exposure Assessment for Air Contaminants. Boca Raton, Taylor and Francis, 2005.

Sahmel, J., Devlin, K., Paustenbach, D., Hollins, D., and Gaffney, S.: The role of exposure reconstruction in occupational human health risk assessment: Current methods and a recommended framework. Crit. Rev. Toxicol. 40:799-843, 2010.

Sala, C., Mosconi, G., Bacis, M., Bernabeo, F., Bay, A., and Sala, O.: Cobalt exposures in ‘hard metal’ and diamonds grinding tools manufacturing and in grinding processes. Sci. Total Environ. 150:111-116, 1994.

Scansetti, G., Lamon, S., Talarico, S., Botta, G.C., Spinelli, P., Sulotto, F., and Fantoni, F.: Urinary cobalt as a measure of exposure in the hardmetal industry. Int. Arch. Occup. Environ. Health 57:19-26, 1985.

Scansetti, G., Botta, G.C., Spinelli, P., Reviglione, L., and Ponzetti, C.: Absorption and excretion of cobalt in the hardmetal industry. Sci. Total Environ. 150:141-144, 1994.

Scansetti, G., Maina, G., Botta, G. C., Bambace, P., and Spinelli, P.: Exposure to cobalt and nickel in the hard-metal production industry. Int. Arch. Occup. Environ. Health 71:60-63, 1998.

Schneider, S.: Past approaches to retrospective epidemiological occupational exposure assessment: The use and misuse of exposure assessment. Appl. Occup. Environ. Hyg. 6:547-549, 1991.

CITED LITERATURE (continued)

Seixas, N.S. and Checkoway, H.: Exposure assessment in industry specific retrospective occupational epidemiology studies. Occup. Environ. Med. 52:625-633, 1995.

Seixas, N.S., Moulton, L.H., Robins, T.G., Rice, C.H., Attfield, M.D., and Zellers, E.T.: Estimation of cumulative exposures for the National Study of Coal Workers' Pneumoconiosis. Appl. Occup. Environ. Hyg. 6:1032-1041, 1991.

Singh, A. and Nocerino, J.: Robust estimation of mean and variance using environmental data sets with below detection limit observations. Chemometr. Intell. Lab. 60:69-86, 2002.

Skaugset, N.P., Ellingsen, D.G., Notø, H., Jordbekken, L., and Thomassen, Y.: Intersampler field comparison of Respicon®, IOM and closed-face 25mm personal aerosol samplers during primary production of aluminum. Ann. Occup. Hyg. 57:1054-1064, 2013.

Smith, E.N.: Tungsten carbide: Crystals by the ton. J. Cryst. Growth. 89:75-79, 1988.

Sorahan, T. and Esmen, N.A.: Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000. Occup. Environ. Med. 61:108-116, 2004.

Stefaniak, A.B., Day, G.A., Harvey, C.J., Leonard, S.S., Schwegler-Berry, D.E., Chipera, S.J., Sahakian, N.M., and Chisholm, W.P.: Characteristics of dusts encountered during the production of cemented tungsten carbides. Ind. Health 45:793-803, 2007.

Stefaniak, A.B., Abbas, M., and Day, G.A.: Characterization of exposures among cemented tungsten carbide workers. Part I: Size-fractionated exposures to airborne cobalt and tungsten particles. J. Expo. Sci. Environ. Epidemiol. 19:475-491, 2009.

Sutherland J.W., Kulur, V.N., and King, N.C.: An experimental investigation of air quality in wet and dry turning. CIRP Ann. Manuf. Technol. 49:61-64, 2000.

Symanski, E., Chang, C., and Chan, W.: Long-term trends in exposures to nickel aerosols. Am. Ind. Hyg. Assoc. J. 61:324-333, 2000.

Symanski, E., Kupper, L., and Rappaport, S.: Comprehensive evaluation of long-term trends in occupational exposure: Part I. Description of the database. Occup. Environ. Med. 55:300-309, 1998.

Symanski, E., Kupper, L.L., Kromhout, H., and Rappaport, S.M.: An investigation of systemic changes in occupational exposure. Am. Ind. Hyg. Assoc. J. 57:724-735, 1996.

"Rules." Tennessee Department of Labor and Workforce Development (TDLWD). Occupational Safety and Health Standards for General Industry. 2002.

CITED LITERATURE (continued)

Teschke, K., Marion, S.A., van Zuylen, M.J.A., and Kennedy, S.M.: Maintenance of stellite and tungsten carbide saw tips: Determinants of exposure to cobalt and chromium. Am. Ind. Hyg. Assoc. J. 56:661-669, 1995.

Torra, M., Fernandez, J., Rodamilans, M., Navarro, A., and Corbeila, J.: Biological monitoring of cobalt exposure: results in a non-exposed population and on workers of a hard metal manufacture. Trace Elem. Electroly. 22:174-177, 2005.

Tsai, P.J., Vincent, J.H., Wahl, G., and Maldonado, G.: Occupational exposure to inhalable and total aerosol in the primary nickel production industry. Occup. Environ. Med. 52:793-799, 1995.

Ulfvarson, U.: Limitations to the use of employee exposure data on air contaminants in epidemiologic studies. Int. Arch. Occup. Environ. Health 52:285-200, 1983.

Verma DK, Shaw DS, Shaw ML, Julian JA, McCollin SA, des Tombe K.: An evaluation of analytical methods, air sampling techniques, and airborne occupational exposure of metalworking fluids. J Occup Environ Hyg. 3:53-66, 2006.

Vincent, J.H., Brosseau, L.M., Ramachandran, G., Tsai, P.J., Spear, T.M., Werner, M.A., and McCullough, N.V.: Current issues in exposure assessment for workplace aerosols. Ann. Occup. Hyg. 41:607-614, 1997.

Wacholder, S., Dosemeci, M., and Lubin, J.H: Blind assessment of exposure does not always prevent differential misclassification. Am. J. Epidemiol. 134:433-437, 1991.

Wang, Y., Wang, S., Jia L., Zhang, L., Ba, J., Han, D., Yu, C., and Wu, Y.: Nickel-refining fumes induced DNA damage and apoptosis of NIH/3T3 cells via oxidative stress. Int. J. Environ. Res. Public Health 13(7), 629. http://doi.org/10.3390/ijerph13070629.

Werner, M.A., Spear, T.M., and Vincent, J.H.: Investigation into the impact of introducing workplace aerosol standards based on the inhalable fraction. Analyst 121:1207-1214, 1996.

Werner, M.A., Vincent, J.H., Thomassen, Y., Hetland, S., and Berge, S.: Inhalable and “total” metal and metal compound aerosol exposures for nickel refinery workers. Occup. Hyg. 5:93-109, 1999.

Wild, P., Perdrix, A., Romazini, S., Moulin, J., and Pellet, F.: Lung cancer mortality in a site producing hardmetals. Occup. Environ. Med. 57:568-573, 2000.

Woskie, S.R., Smith, T.J., Hammond, S.K., and Hallock, M.H.: Factors affecting worker exposures to metal-working fluids during automotive component manufacturing. Appl. Occup. Environ. Hyg. 9:612-621, 1994.

CITED LITERATURE (continued)

Yamada, Y., Kido, T., Honda, R., Ishizaki, M., Tsuritani, I., Yamaya, H., Nogawa, K.: Analysis of dusts and evaluation of dust exposure in a hard metal factory. Ind Health. 25:1-10, 1987.

Yue, Y., Gunter, K.L., Michalek, D.J., and Sutherland, J.W.: An examination of cutting fluid mist formation in turning. Transactions of NAMRI/SME 27:221-226, 1999.

APPENDICES

APPENDIX A: Hardmetal Processes and Copyright Permission

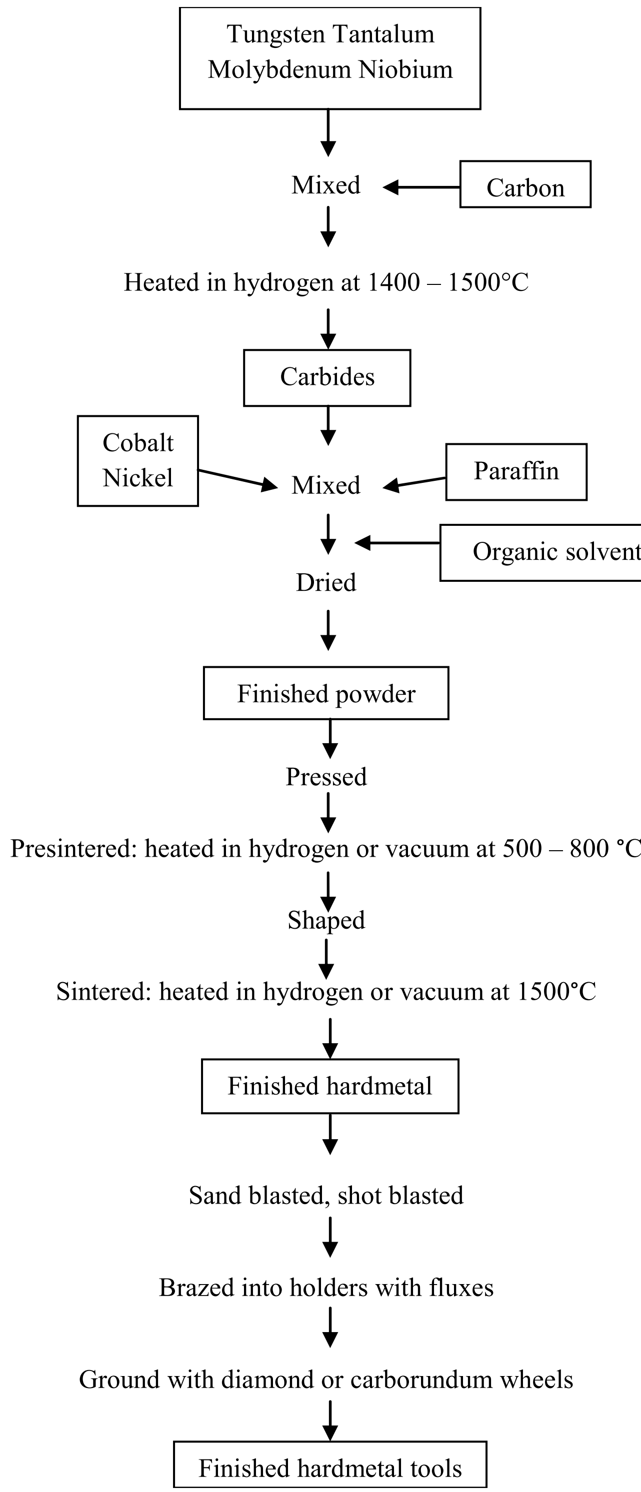

Figure 2. General steps in tungsten carbide powder and tool production. Adapted by permission from BMJ Publishing Group Limited. [Respiratory diseases in hard metal workers: an occupational hygiene study in a factory, Kusaka et al., 43, 474-485, 2017.]

APPENDIX A: Hardmetal Processes and Copyright Permission (continued)

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Title:	Respiratory diseases in hard metal workers: an occupational hygiene study in a factory.
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Appendix A: Hardmetal Processes and Copyright Permission (continued)

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APPENDIX B

TABLE VI

EUROPEAN OCCPATIONAL EXPOSURE LIMITS BY COUNTRY, AGENT, AND TIME PERIOD

Country	Cobalt[a] (mg/m^3)	Time Period	Reference[b]	Tungsten[a] (mg/m3)	Time Period	Reference	Nickel[a] (mg/m3)	Time Period	Reference
Austria	0.05	1985 - 2012	1	5.0	1985 - 2012	1	0.5	1996 - 2012	3
Germany	0.5	1990	2	--	--	--	0.5	1992	2
Sweden	0.1	1974 - 1977	1, 3	5.0	1990	2	0.01	1974 - 1977	1, 3
	0.05	1978 - 2010	1, 2, 3	--	--	--	0.5	1978 - present	1, 2, 3
	0.02[c]	2011 - present	1, 3	--	--	--	--	--	--
Great Britain[d]	0.1[e]	1969 - 2013	1, 2, 3	5[e]	1969 - 2011	1, 2, 3	1[e]	1969 - 1989	3
	--	--	--	--	--	--	0.5[c]	1990 - 2011	1, 2, 3

[a]All values refer to total aerosols of metal/elemental/insoluble forms unless otherwise noted.

[b]References: 1 - Industrial hygiene measurement database entry; 2 - Threshold Limit Value Documentation (ACGIH, 1991);
3 - Personal communication.

[c]Inhalable fraction.

[d]Per a United Kingdom investigator the limits shown apply to Great Britain only, where the two United Kingdom sites are located.

[e]Expressed as inhalable fraction beginning 1987.

APPENDIX C: Industrial Hygiene Database Fields

1) Job class (assigned by country-specific investigators)
2) Process/operation sampled (shaping, grinding, etc.)
3) Sample date
4) Company
5) Country
6) Plant
7) Department title/number
8) Building/area
9) Exposure agent
10) Chemical Abstracts Service (CAS) number
11) Agent concentration
12) Units
13) Task during sampling
14) Equipment/machine/tools
15) Production information (units made, etc.)
16) Climatic information (temperature, humidity, etc.)
17) Job title
18) Job code
19) Shift
20) Sampling time
21) Air volume
22) Type of sample (full shift, task, partial shift)
23) Sample technique (personal, area)
24) Particle size fraction (respirable, thoracic, inhalable, total)
25) Occupational exposure limit (e.g.., TLV, PEL, etc.)
26) Reason for sample (compliance, complaint, emergency, other)
27) Worker selection basis (random, convenience, presumed high exposure)
28) Survey performed by (consultant, company, etc.)
29) Sampling device type
30) Sampling collection media
31) Analytical or reference method (of sample analysis)
32) Limit of quantification of analytical method
33) Laboratory quality assurance procedures (external certification, in-house, none)
34) Engineering controls on process/activity
35) Respiratory protection worn (Y/N)
36) Gloves worn (Y/N)
37) Protective clothing worn (Y/N)
38) Eye/face protection worn (Y/N)

APPENDIX D

TABLE VII

QUALITATIVE FACTOR LEVEL, CODING, AND SAMPLE SIZE

Factor	Code	Level	N
Country	1	Austria	74
	2	Germany	325
	3	Sweden	1866
	4	United Kingdom	1272
	5	US	4799
Company[a]	1 - 3	--	8336
Plant[a]	1 - 21	--	8336
Plant type	1	Manufacturing	1437
	2	Powder mixing/blending and manufacturing	3540
	3	Powder production and manufacturing	3359
Age of facility	1	Open before 1960	5424
	2	Open during or after 1960	2912
Major job class category	1	Background/intermediate	636
	2	Exposed manufacturing	5104
	3	Exposed powder production and handling	2596
Production phase	1	Background/intermediate/no hardmetal powder or part exposure	708
	2	Post-sintering	1966
	3	Pre-sintering	5662
Particulate fraction	1	Total aerosol	7014
	2	Inhalable fraction	1322

[a]Company and plant must remain de-identified, therefore they were not broken down in this table.
[b]All TLVs are given as total aerosol unless otherwise noted.
[c]Limited measurements taken from 1963 - 1967 (n=3) were combined with subsequent period.

APPENDIX D (continued)

TABLE VII (continued)

QUALITATIVE FACTOR LEVEL, CODING, AND SAMPLE SIZE

Factor	Code	Level	N
Measurement analysis period	1	1965 - 1991, atomic absorption predominant	1480
	2	1992 - 1999, mix of atomic absorption, inductively coupled plasma, and x-ray diffraction methods	2059
	3	2000 onward, inductively coupled plasma predominant	4797
Threshold limit value (TLV)	1[c]	Cobalt, 1963 - 1967 (0.5 mg/m^3) and 1968 - 1986 (0.1 mg/m^3)	548
time period[b]	2	Cobalt, 1987 - 1994 (0.05 mg/m^3)	974
	3	Cobalt, 1995 - present (0.02 mg/m^3)	4653
	4	Tungsten, 1969 - present (5.0 mg/m^3)	1023
	5	Nickel, 1966 - 1997 (1.0 mg/m^3)	495
	6	Nickel, 1998 - present (1.5 mg/m^3, inhalable fraction)	643

[a]Company and plant must remain de-identified, therefore they were not broken down in this table.
[b]All TLVs are given as total aerosol unless otherwise noted.
[c]Limited measurements taken from 1963 - 1967 (n=3) were combined with subsequent period.

APPENDIX E

TABLE VIII

NUMBER AND PERCENT OF INDUSTRIAL HYGIENE MEASUREMENTS BY YEAR AND ANALYSIS METHOD

Year	Atomic Absorption (AA)	AA %	Inductively coupled plasma (ICP)	ICP %	X-ray Fluorescence (XRF)	XRF %	Total by Year
1965	3	100					3
1966							
1967							
1968							
1969							
1970	10	100					10
1971	8	100					8
1972							
1973							
1974	11	100					11
1975							
1976							
1977	1	100					1
1978	95	100					95
1979	55	100					55
1980	49	100					49
1981	28	100					28
1982	29	100					29
1983	95	99	1	1			96
1984	81	100					81
1985	46	100					46
1986	116	100					116
1987	99	100					99
1988	157	99			1	1	158
1989	139	100					139
1990	73	100					73
1991	119	100					119
1992	23	18	28	21	80	61	131
1993	15	39	14	37	9	24	38
1994	99	32	46	15	165	53	310
1995	108	77	32	23			140

APPENDIX E (continued)

TABLE VIII (continued)

NUMBER AND PERCENT OF INDUSTRIAL HYGIENE MEASUREMENTS BY YEAR AND ANALYSIS METHOD

Year	Atomic Absorption (AA)	AA %	Inductively coupled plasma (ICP)	ICP %	X-ray Fluorescence (XRF)	XRF %	Total by Year
1996	111	63	54	31	11	6	176
1997	114	51	67	30	41	18	222
1998	148	38	73	19	167	43	388
1999	82	29	130	46	71	25	283
2000	38	22	97	57	34	20	169
2001	58	34	109	64	2	1	169
2002	36	21	109	62	30	17	175
2003	10	4	211	84	29	12	250
2004	85	19	331	73	36	8	452
2005	139	32	240	55	58	13	437
2006	49	9	433	83	39	7	523
2007	26	6	352	82	52	12	430
2008			487	100			487
2009			141	98	3	2	144
2010			166	100			166
2011			182	91	18	9	200
2012			162	91	17	9	179
2013			46	100			46
Total by Method	2355	--	3511	--	863		6729

APPENDIX F: Project Approvals

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Determination Notice
Research Activity Does Not Involve "Human Subjects"

October 8, 2007

Nurtan A. Esmen, Ph.D.
Environmental and Occupational Health
2121 W Taylor Street
Env & Occup Health Science, M/C 922
Chicago, IL 60612
Phone: (312) 413-9113 / Fax: (312) 413-9898

RE: Research Protocol # 2007-0693
"Tungsten Industry Pilot Study"

Dear Dr. Esmen:

The above proposal was reviewed on October 8, 2007 by OPRS staff/members of IRB #2. From the information you have provided, the proposal does not appear to involve "human subjects" as defined in 45 CFR 46. 102(f).

The specific definition of human subject under 45 CFR 46.102(f) is:

> *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
>
> (1) data through intervention or interaction with the individual, or
> (2) identifiable private information.
>
> *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

All the documents associated with this proposal will be kept on file in the OPRS and a copy of this letter is being provided to your Department Head for the department's research files.

APPENDIX F: Project Approvals (continued)

2007-0693 Page 2 of 2 October 8, 2007

If you have any questions or need further help, please contact the OPRS office at (312) 996-1711 or me at (312) 355-2908. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Charles W. Hoehne
Assistant Director, IRB # 2
Office for the Protection of Research Subjects

cc: Rosemary Sokas, MD, MOH, Environmental and Occupational Health, M/C 922

APPENDIX F: Project Approvals (continued)

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Continuing Review

March 25, 2016

Nurtan A. Esmen, Ph.D.
Environmental and Occupational Health
2121 W Taylor Street
Env & Occup Health Science, M/C 922
Chicago, IL 60612
Phone: (312) 413-9113 / Fax: (312) 413-9898

RE: Protocol # 2008-0949
"Tungsten Carbide Worker Epidemiology Study"

Dear Dr. Esmen:

Your Continuing Review was reviewed and approved by the Expedited review process on March 25, 2016. You may now continue your research.

Please note the following information about your approved research protocol:

Protocol Approval Period: April 12, 2016 - April 12, 2017
Approved Subject Enrollment #: 30000 (data analysis from 9,405 subjects)
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC, University of Pittsburgh Medical Center
Sponsor: U of Pittsburgh
PAF#: 2011-05972
Grant/Contract No: Not available
Grant/Contract Title: Tugnsten Carbide with Cobalt Binder: An Historical Cohort and Nested Case-Control Study

Research Protocol(s):

a) Scope of Work: Tungsten Carbide Worker Epidemiology Study; Version 2; 08/21/2015
b) Proposal for Research: Tungsten Carbide Worker Epidemiology Study - Phase 3, Part 1

Recruitment Material(s):

a) N/A- Limited to data analysis only.

Informed Consent(s):

a) N/A- Limited to data analysis only.

APPENDIX F: Project Approvals (continued)

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific category:

(7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
03/23/2016	Continuing Review	Expedited	03/25/2016	Approved

Please remember to:

→ Use your **research protocol number** (2008-0949) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-9680. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Jovana Ljuboje
IRB Coordinator, IRB #2
Office for the Protection of Research Subjects

cc: Linda S. Forst, Environmental and Occupational Health, M/C 922
OVCR Administration, M/C 672

APPENDIX G

TABLE IX

NUMBER OF INDIVIDUALS AND WORKING-YEARS WITHIN EACH JOB CLASS

Job Class Number	Job Class Name	Number of Workers in Job Class[a,b] US[d]	Austria	Germany	Sweden	United Kingdom	Total	Working Years (All Workers)[a,c]
	Background and Support Operations							
00	Background	1,187	245	623	1,912	248	4,215	31,062
01	Laboratory/Research & Development	238	144	32	1,901	110	2,425	10,817
02	Supervisory	487	319	0	297	4	1,107	8,280
03	Engineering	433	59	0	413	63	968	6,306
04	Trades	1,912	88	495	3,341	136	5,972	32,180
05	Material handling	497	30	2,218	508	34	3,287	20,447
06	Assembly	21	0	0	986	3	1,010	5,578
07	Mark/pack	582	50	200	1,414	19	2,265	8,912
08	Inspection	711	189	823	808	47	2,578	15,646
	General Production Operations							
09	Powder weigh	21	0	8	8	0	37	171
10	Powder mix/blend	1	0	248	0	0	249	2,092
11	Powder sieve/screen	1	0	0	0	0	1	0
12	Pelletize/granulate	42	0	0	2	0	44	194
13	Powder packaging/transfer	0	0	2	10	0	12	85
14	Press set-up	107	39	0	83	80	309	2,195
15	Press	1,028	146	883	1,285	73	3,415	14,544
16	Shape	497	224	209	20	37	987	7,100

[a]All counts of individuals and working-years through 12/31/2008 only.

[b]Individuals may have more than one job over time and thus be counted in more than one job class.

[c]Working-years is the total time all individuals were employed in the job class.

[d]Reflects workers at the 8 US plants included in the epidemiological analyses conducted by the University of Pittsburgh.

APPENDIX G (continued)

TABLE IX (continued)

NUMBER OF INDIVIDUALS AND WORKING-YEARS WITHIN EACH JOB CLASS

Job Class Number	Job Class Name	Number of Workers in Job Class[a,b] US[d]	Austria	Germany	Sweden	United Kingdom	Total	Working Years (All Workers)[a,c]
	General Production Operations							
17	Extrude	39	174	73	5	24	315	1,493
18	Cold isostatic press/slug form	13	3	37	3	36	92	393
19	Furnace set-up	96	0	9	0	3	108	453
20	Furnace	466	147	402	179	65	1,259	8,323
21	Computer numerical control operation	151	0	266	28	24	469	2,074
22	Hone/polish/lap	343	35	0	637	2	1,017	5,037
23	Grind	1,503	345	1,657	2,122	137	5,764	35,338
24	Slow moving operations	48	175	0	581	25	829	2,939
25	Electro-discharge machining	14	8	0	9	2	33	163
26	Blast	84	16	121	89	1	311	1,080
27	Coat	341	60	283	561	5	1,250	7,272
	Tungsten Carbide Powder Production Operations							
28	Ball mill	35	0	0	1	0	36	191
29	Fitz mill	0	0	0	0	0	0	0
30	Attritor	0	0	0	0	0	0	0
31	Spray dry	44	0	0	61	31	136	733
32	Mill and spray dry	188	0	0	0	0	188	714

[a]All counts of individuals and working-years through 12/31/2008 only.

[b]Individuals may have more than one job over time and thus be counted in more than one job class.

[c]Working-years is the total time all individuals were employed in the job class.

[d]Reflects workers at the 8 US plants included in the epidemiological analyses conducted by the University of Pittsburgh.

APPENDIX G (continued)

TABLE IX (continued)

NUMBER OF INDIVIDUALS AND WORKING-YEARS WITHIN EACH JOB CLASS

Job Class Number	Job Class Name	Number of Workers in Job Class[a,b] US[d]	Austria	Germany	Sweden	United Kingdom	Total	Working Years (All Workers)[a,c]
	Tungsten Carbide Powder Production Operations							
33	Ammonium-paratungstate process	0	0	29	0	0	29	150
34	Thermit process	304	0	0	0	0	304	1,133
52	WC powder production unspecified	9	0	0	176	33	218	845
	Additional Operations							
35	Weld	72	0	0	0	0	72	342
36	Braze	539	3	0	120	1	663	2,795
37, 65	Rapid omni-directional compaction, Foundry	34	0	0	0	0	34	171
39	Powder room operations	302	101	0	0	128	531	2,530
40	Ceramic grind	3	0	16	0	0	19	45
41	Ceramic weigh	0	0	62	1	0	63	404
42	Dry grind	6	0	593	0	0	599	2,401
43	Recycling	66	0	0	0	20	86	410
44	Mechanical production	892	0	252	0	0	1,144	5,410
45	Graphite service	7	6	4	0	0	17	51
46	Heavy metal powder production	0	0	20	631	0	651	1,124
47	Medical engineering	0	0	98	0	0	98	758

[a]All counts of individuals and working-years through 12/31/2008 only.

[b]Individuals may have more than one job over time and thus be counted in more than one job class.

[c]Working-years is the total time all individuals were employed in the job class.

[d]Reflects workers at the 8 US plants included in the epidemiological analyses conducted by the University of Pittsburgh.

APPENDIX G (continued)

TABLE IX (continued)

NUMBER OF INDIVIDUALS AND WORKING-YEARS WITHIN EACH JOB CLASS

Job Class Number	Job Class Name	Number of Workers in Job Class[a,b] US[d]	Austria	Germany	Sweden	United Kingdom	Total	Working Years (All Workers)[a,c]
	Additional Operations							
48	Metals (white collar)	0	10	0	0	0	10	64
49	Metals (blue collar)	0	59	0	0	0	59	270
50	Press/form/sinter	0	0	0	34	0	34	101
51	Hone/coat	0	0	0	0	0	0	0
53	W production	0	0	0	821	0	821	1,291
54	Carbon production	0	0	0	0	0	0	0
55	WC parts production unspecified	631	0	0	136	130	897	3,254
56	Rolls unspecified	0	0	0	78	0	78	215
57	Rolls press	0	0	0	10	0	10	139
58	Rolls shape	0	0	0	5	0	5	39
59	Rolls sinter	0	0	0	6	0	6	74
60	Rolls grind	0	0	0	10	0	10	143
61	Rolls inspect/pack	0	0	0	0	0	0	0
62	Hydrogen gas production	0	0	0	83	0	83	295
63	Ceramic other	0	0	0	76	0	76	256
64	WC powder/parts production unspecified	95	0	0	1,411	281	1,787	13,846

[a]All counts of individuals and working-years through 12/31/2008 only.

[b]Individuals may have more than one job over time and thus be counted in more than one job class.

[c]Working-years is the total time all individuals were employed in the job class.

[d]Reflects workers at the 8 US plants included in the epidemiological analyses conducted by the University of Pittsburgh.

APPENDIX G (continued)

TABLE IX (continued)

NUMBER OF INDIVIDUALS AND WORKING-YEARS WITHIN EACH JOB CLASS

Job Class Number	Job Class Name	Number of Workers in Job Class[a,b] US[d]	Austria	Germany	Sweden	United Kingdom	Total	Working Years (All Workers)[a,c]
				Additional Operations				
66	Tube milling	6	0	0	0	0	6	16
				Other				
75	Blue collar worker[e]	0	0	659	0	0	659	9,100
38, 85	Mine, Leave of absence	207	0	780	0	3	990	2,573
95	Unknown[f]	45	0	0	0	218[g]	45	3,058

[a]All counts of individuals and working-years through 12/31/2008 only.

[b]Individuals may have more than one job over time and thus be counted in more than one job class.

[c]Working-years is the total time all individuals were employed in the job class.

[d]Reflects workers at the 8 US plants included in the epidemiological analyses conducted by the University of Pittsburgh.

[e]No further job classification possible; Germany only.

[f]Only one job per person and no identifying work information.

[g]Does not include 118 United Kingdom workers due to lack of valid work date information.

APPENDIX H: Sampling Time versus Sampling Year

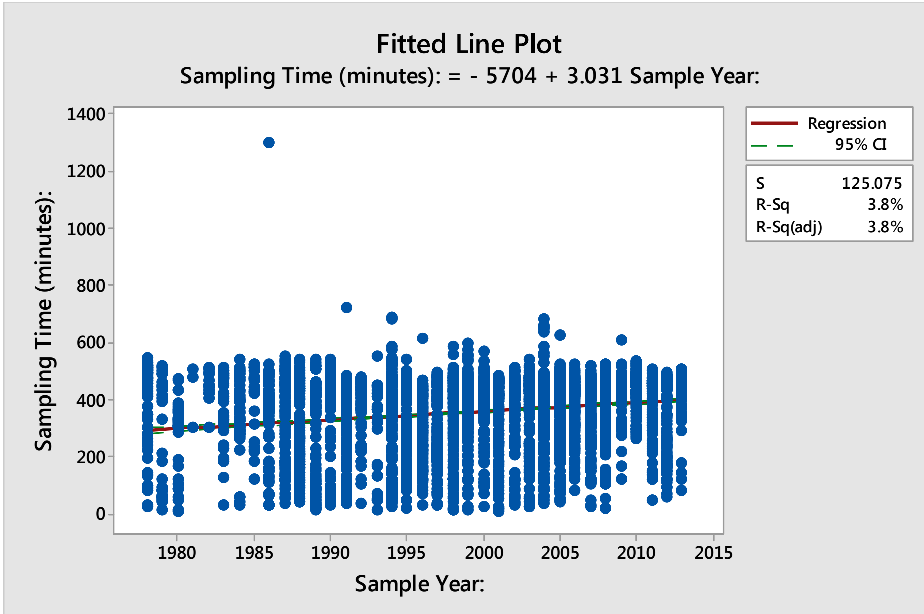

Figure 3. Sampling time versus sampling year for personal cobalt measurements (n = 5,525; $|\rho| = 0.195$).

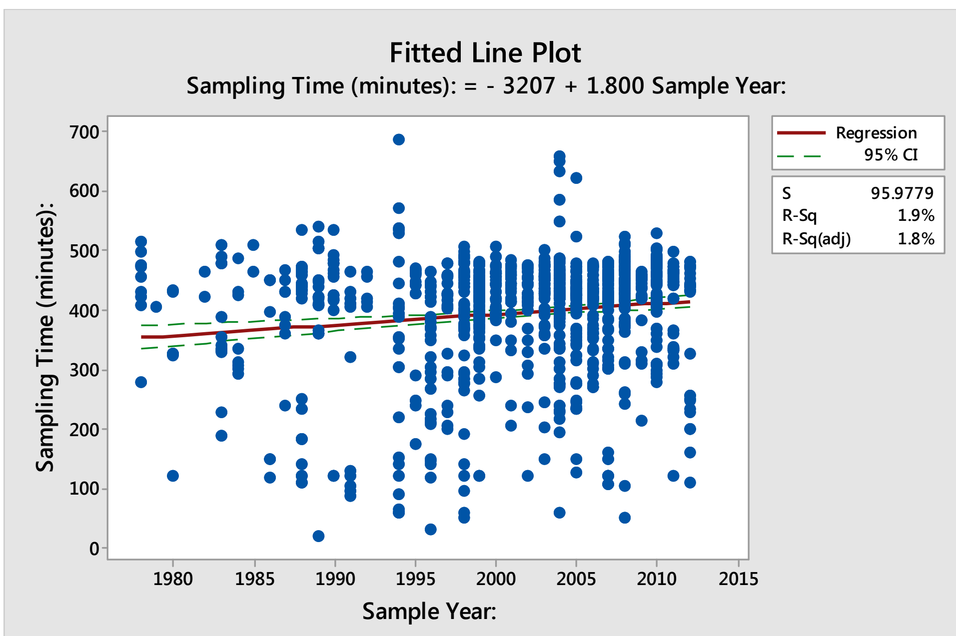

Figure 4. Sampling time versus sampling year for personal cobalt measurements taken during pressing (job class 15) (n = 1,039; $|\rho| = 0.136$).

APPENDIX H: Sampling Time versus Sampling Year (continued)

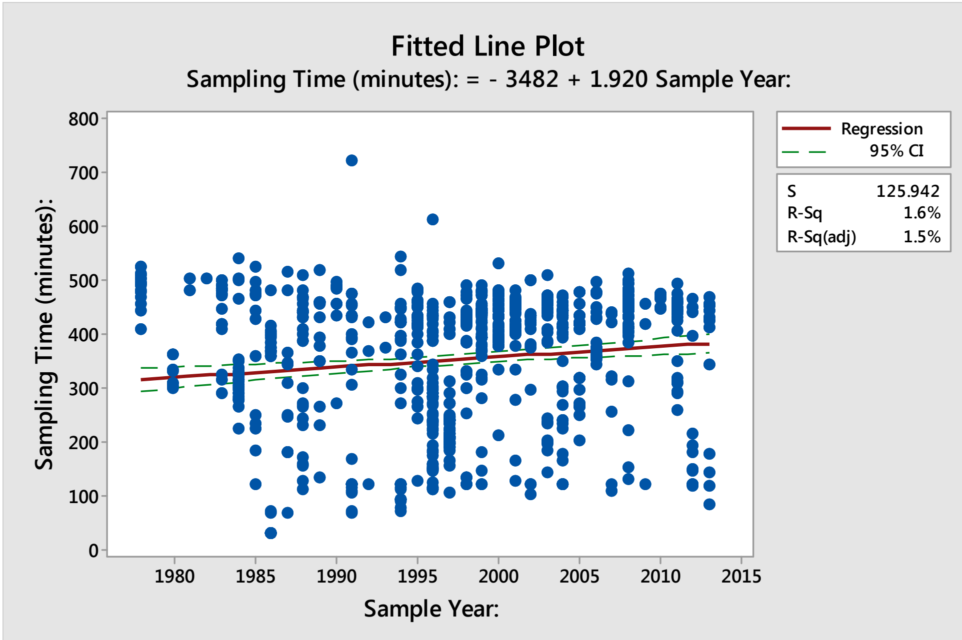

Figure 5. Sampling time versus sampling year for personal cobalt measurements taken during grinding (job class 23) (n = 878; $|\rho|$ = 0.125).

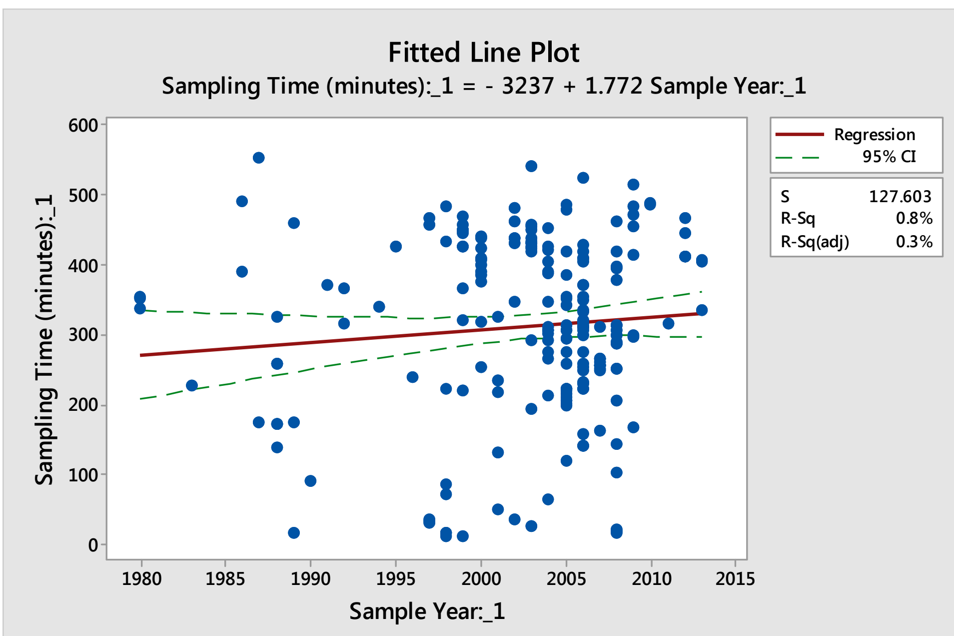

Figure 6. Sampling time versus sampling year for personal cobalt measurements taken during maintenance (job class 04) (n = 210; $|\rho|$= 0.090).

APPENDIX H: Sampling Time versus Sampling Year (continued)

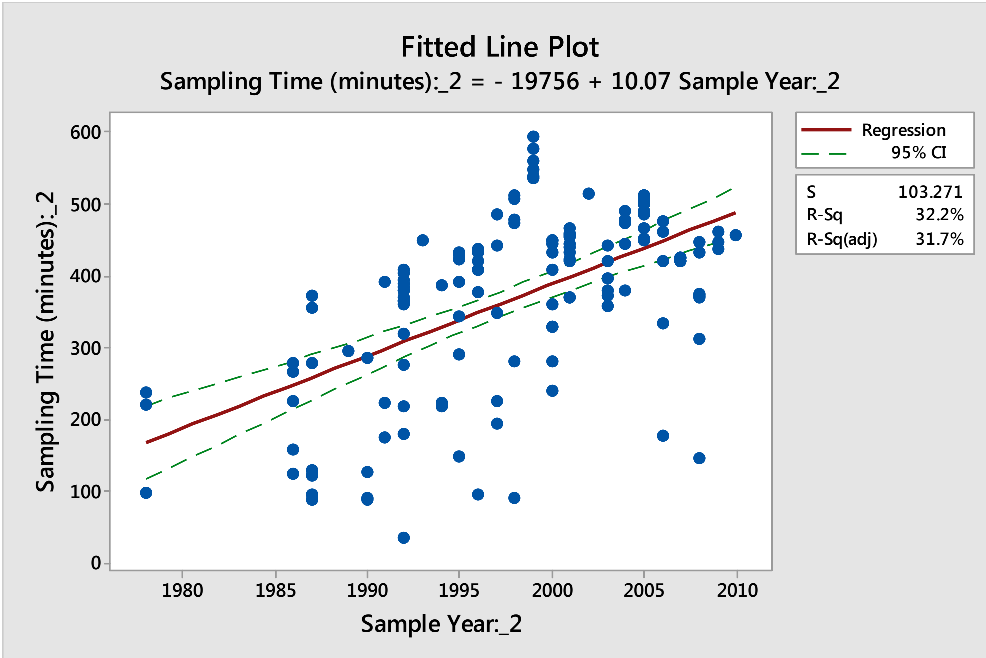

Figure 7. Sampling time versus sampling year for personal cobalt measurements taken during powder milling and drying (job class 32) (n = 141; $|\rho| = 0.567$).

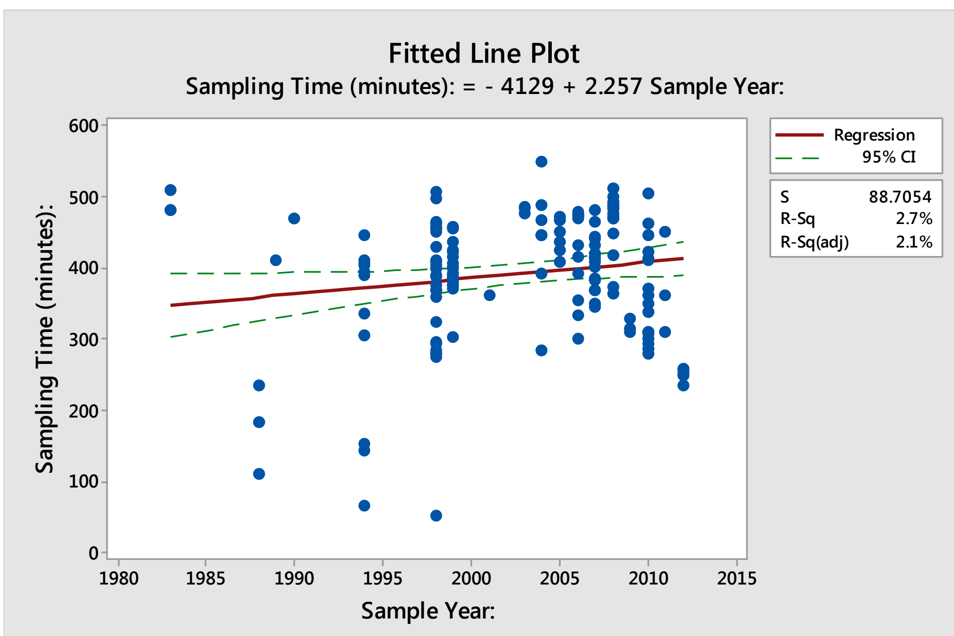

Figure 8. Sampling time versus sampling year for personal tungsten measurements taken during pressing (job class 15) (n = 164; $|\rho| = 0.164$).

APPENDIX H: Sampling Time versus Sampling Year (continued)

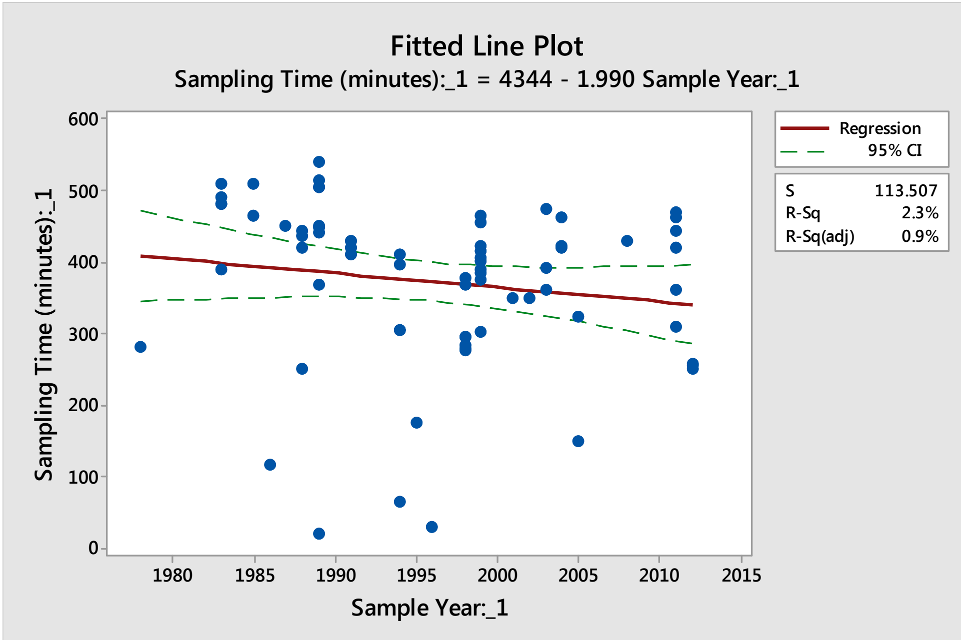

Figure 9. Sampling time versus sampling year for personal nickel measurements taken during pressing (job class 15) (n = 70; $|\rho| = 0.153$).

APPENDIX I: Concentration versus Sampling Time

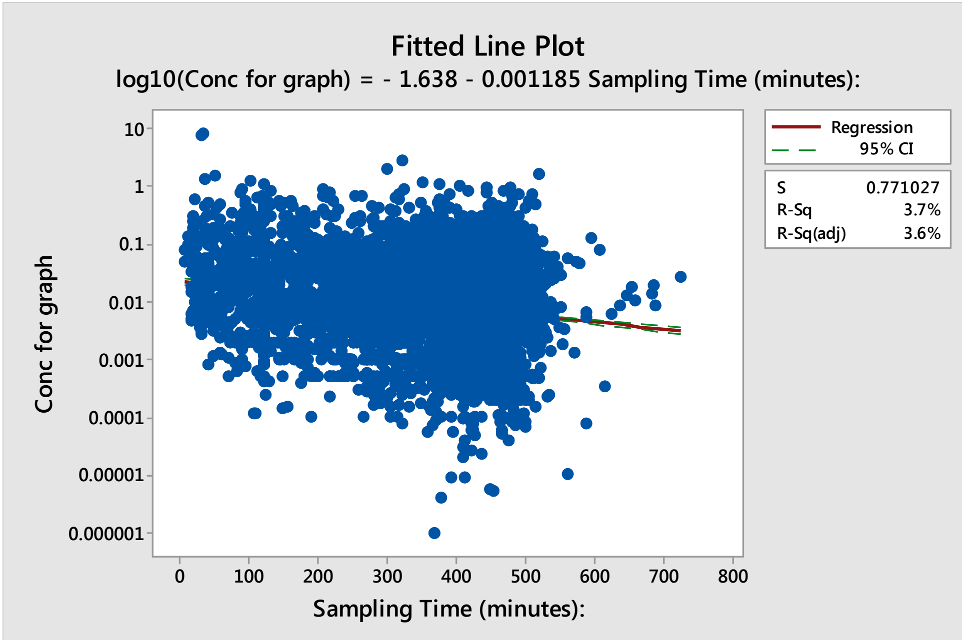

Figure 10. Concentration versus sampling time for personal cobalt measurements (n = 5,506; $|\rho| = 0.192$).

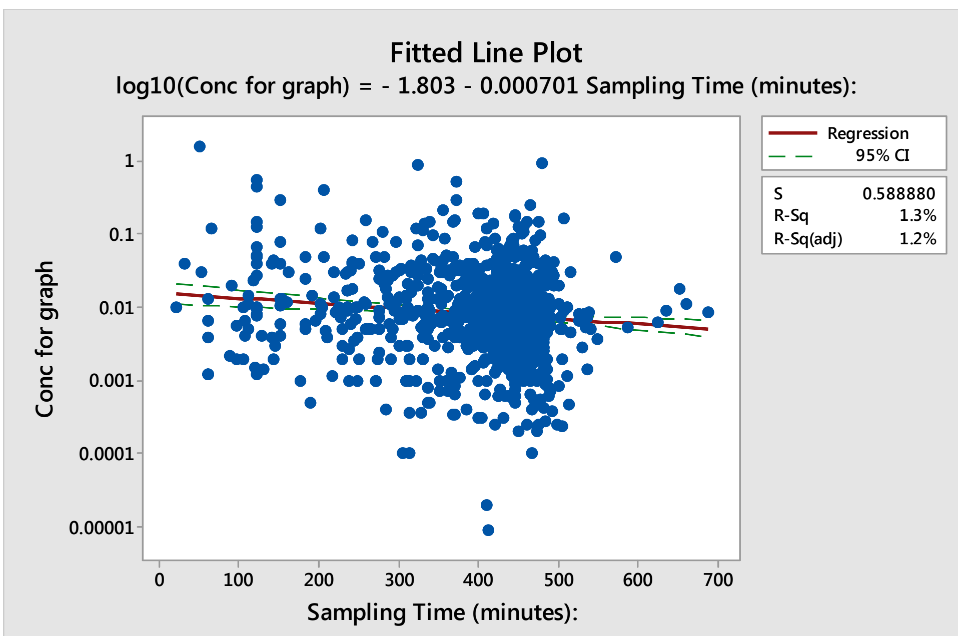

Figure 11. Concentration versus sampling time for personal cobalt measurements taken during pressing (job class 15) (n = 1,038; $|\rho| = 0.113$).

APPENDIX I: Concentration versus Sampling Time (continued)

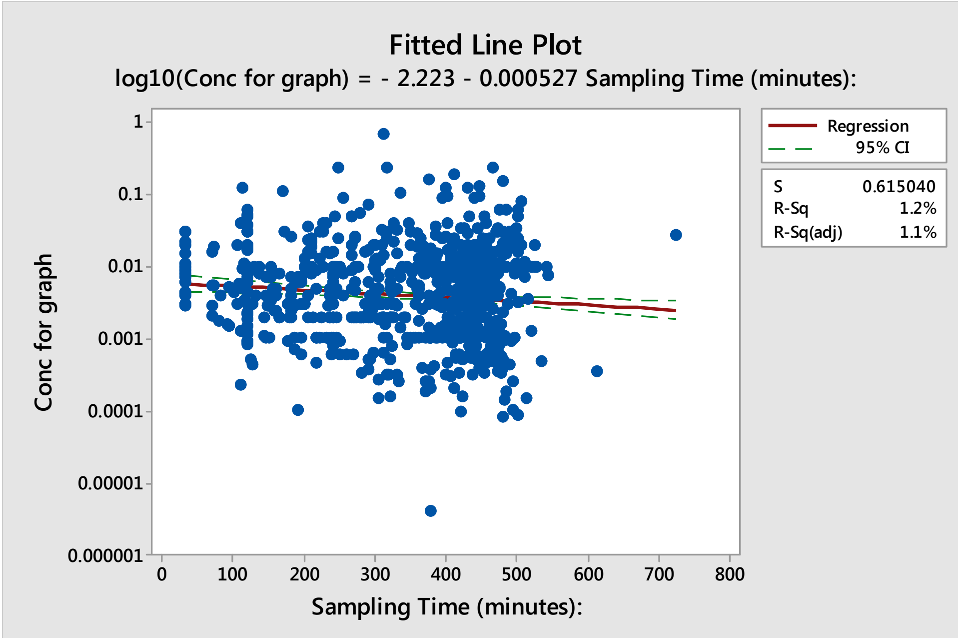

Figure 12. Concentration versus sampling time for personal cobalt measurements taken during grinding (job class 23) (n = 862; $|\rho| = 0.026$).

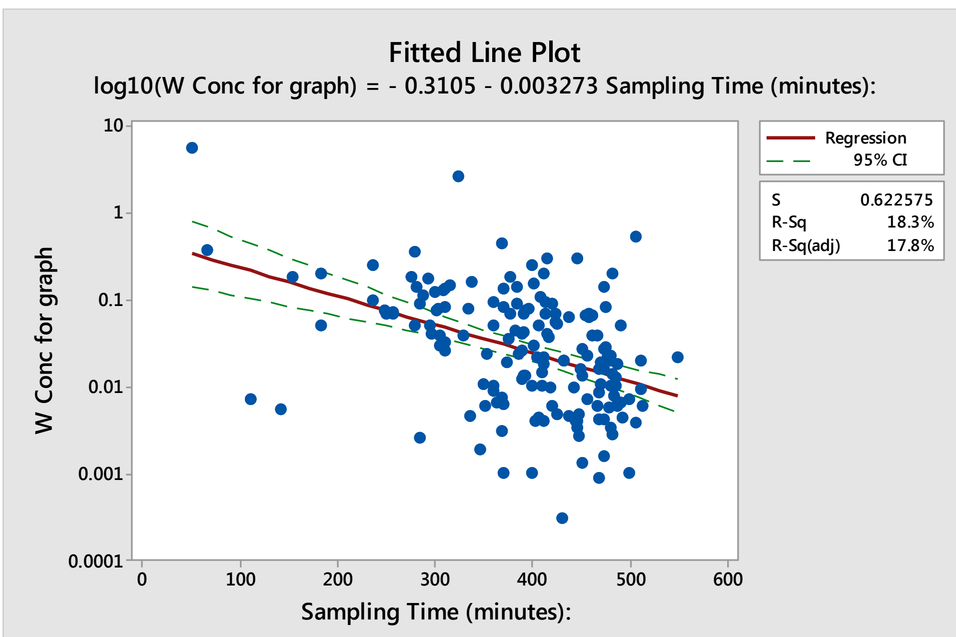

Figure 13. Concentration versus sampling time for personal tungsten measurements taken during pressing (job class 15) (n = 164; $|\rho| = 0.427$).

APPENDIX I: Concentration versus Sampling Time (continued)

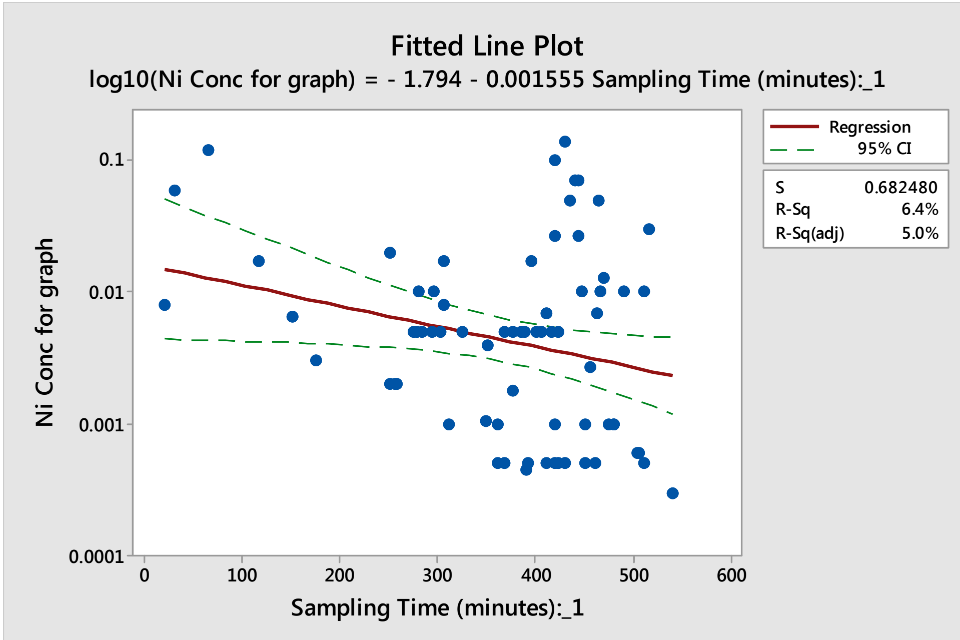

Figure 14. Concentration versus sampling time for personal nickel measurements taken during pressing (job class 15) (n = 70; $|\rho| = 0.253$).

APPENDIX J: Particle Size Descriptive Metrics

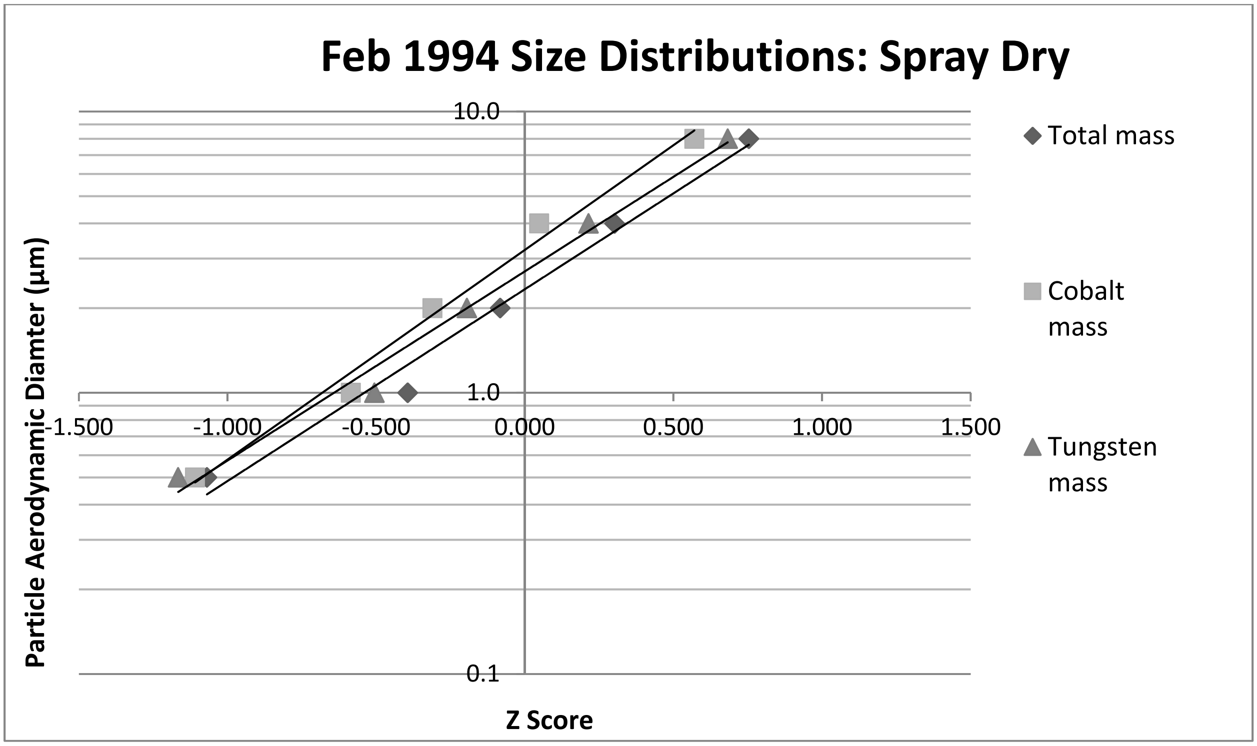

Figure 15. Particle size distributions for cobalt, tungsten, and total aerosol during spray drying operations.

	Equation	R^2	Mass Median Aerodynamic Diameter (µm)	σ_g
Total	$y=2.331e^{1.57x}$	0.98362	2.3	4.8
Cobalt	$y=3.2189e^{1.7158x}$	0.98856	3.2	5.6
Tungsten	$y=2.7004e^{1.5485x}$	0.98691	2.7	4.7

APPENDIX J: Particle Size Descriptive Metrics (continued)

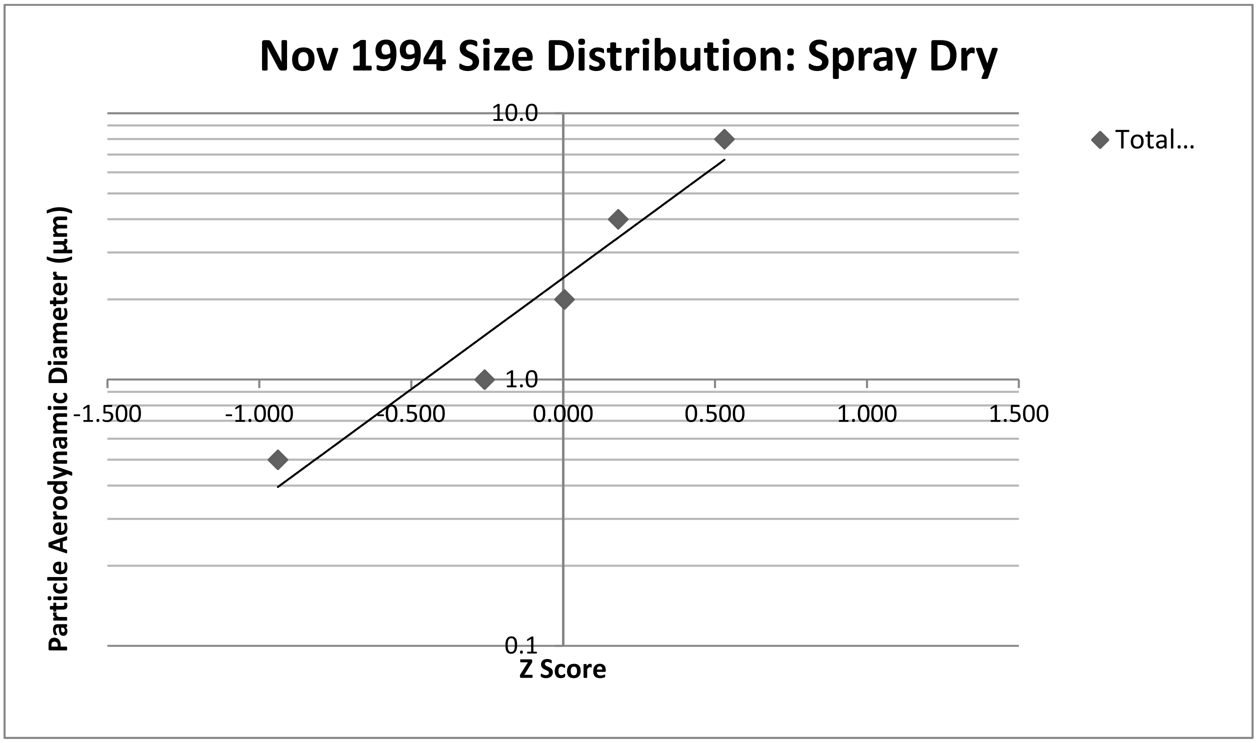

Figure 16. Particle size distributions for total aerosol during spray drying operations.

	Equation	R^2	Mass Median Aerodynamic Diameter (µm)	σ_g
Total	$y=2.4067e^{1.925}$	0.93859	2.4	6.9

APPENDIX J: Particle Size Descriptive Metrics (continued)

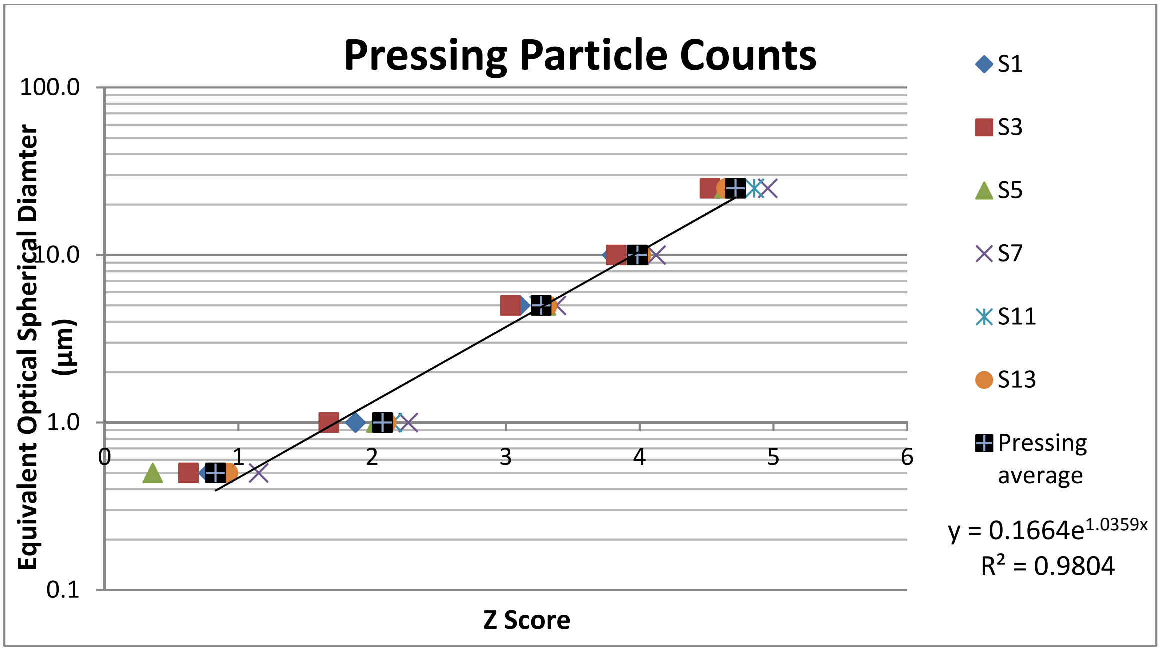

Figure 17. Particle counts for total aerosol during pressing operations.

	Equation	R^2	Mean Equivalent Optical Spherical Diameter (µm) [a]	σ_g	Count Median Aerodynamic Diameter (µm)[b]
Press (S1)	$y=0.1818e^{1.0587x}$	0.9885	0.18	2.9	0.36
Press (S3)	$y=0.2252e^{1.015x}$	0.99118	0.22	2.8	0.44
Press (S5)	$y=0.2539e^{0.9284x}$	0.9547	0.25	2.5	0.50
Press (S7)	$y=0.122e^{1.0679x}$	0.9859	0.12	2.9	0.24
Press (S11)	$y=0.1605e^{1.0313x}$	0.97984	0.16	2.8	0.32
Press (S13)	$y=0.1466e^{1.0699x}$	0.98084	0.15	2.9	0.30
All Pressing	$y=0.1664e^{1.0359x}$	0.98041	0.17	2.8	0.33

[a]Instrument calibrated with polystyrene spheres with a refractive index of 1.59; generates counts for equivalent optical spherical diameters.
[b]Assumed density was 4.0 g/cm^3 per plant contact recommendation.

APPENDIX J: Particle Size Descriptive Metrics (continued)

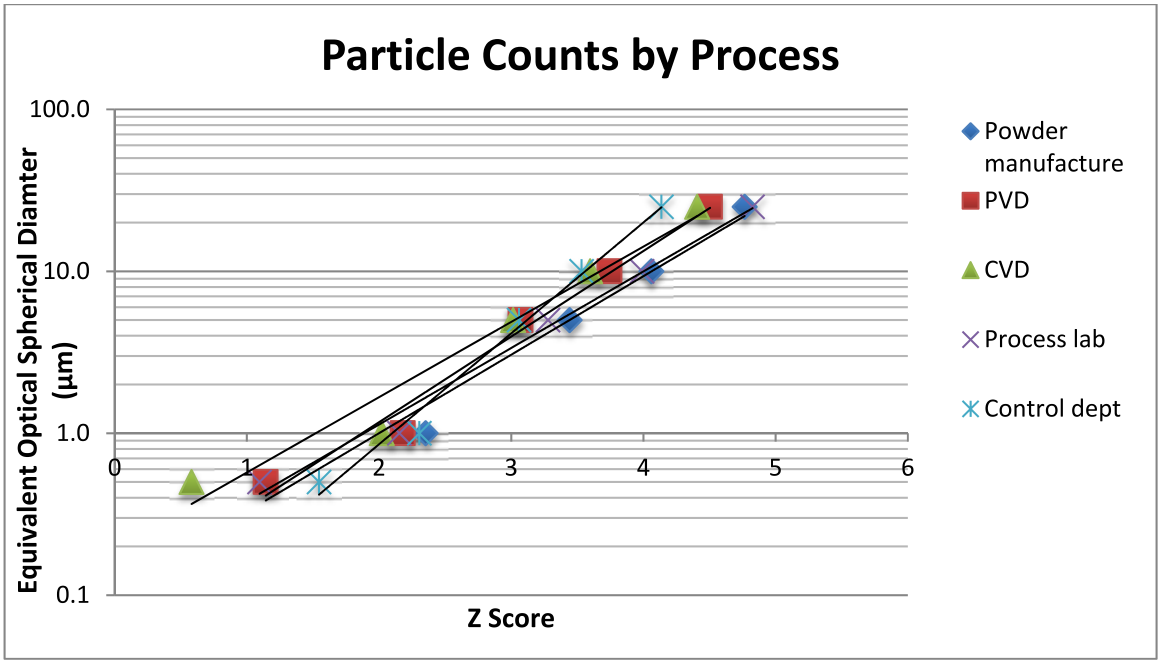

Figure 18. Particle counts for total aerosol during various operations.

	Equation	R^2	Mean Equivalent Optical Spherical Diameter (µm) [a]	σ_g	Count Median Aerodynamic Diameter (µm)[b]
Powder operations	$y=0.1073e^{1.1164x}$	0.97688	0.11	3.1	0.21
Physical vapor deposition (coat)	$y=0.1026e^{1.2171x}$	0.9806	0.10	3.4	0.20
Chemical vapor deposition (coat)	$y=0.1963e^{1.0706}$	0.96104	0.20	2.9	0.39
Process lab	$y=0.1282e^{1.0889x}$	0.98831	0.13	3.0	0.26
Control department	$y=0.0365e^{1.5769x}$	0.98575	0.04	4.8	0.07

[a]Instrument calibrated with polystyrene spheres with a refractive index of 1.59; generates counts for equivalent optical spherical diameters.
[b]Assumed density was 4.0 g/cm^3 per plant contact recommendation.

APPENDIX K: Measurement Lognormality

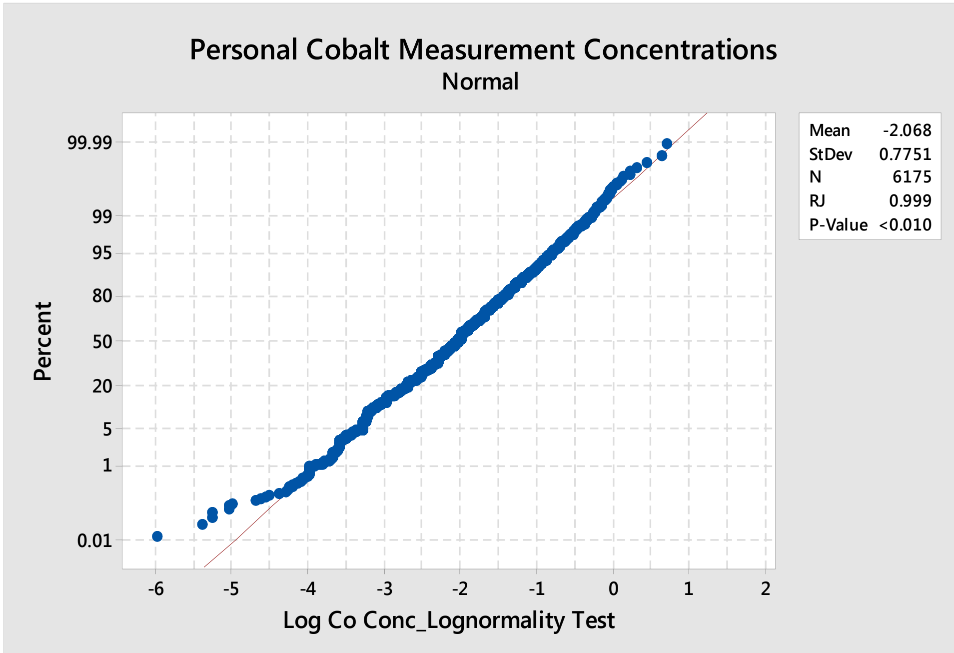

Figure 19. Lognormality graph of personal cobalt measurements.

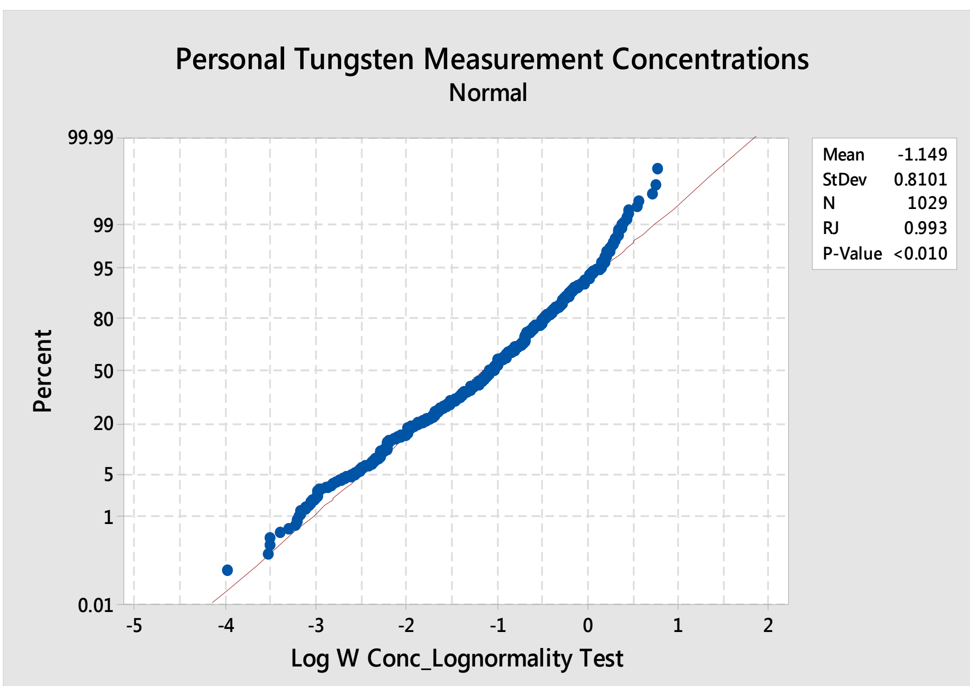

Figure 20. Lognormality graph of personal tungsten measurements.

APPENDIX K: Measurement Lognormality (continued)

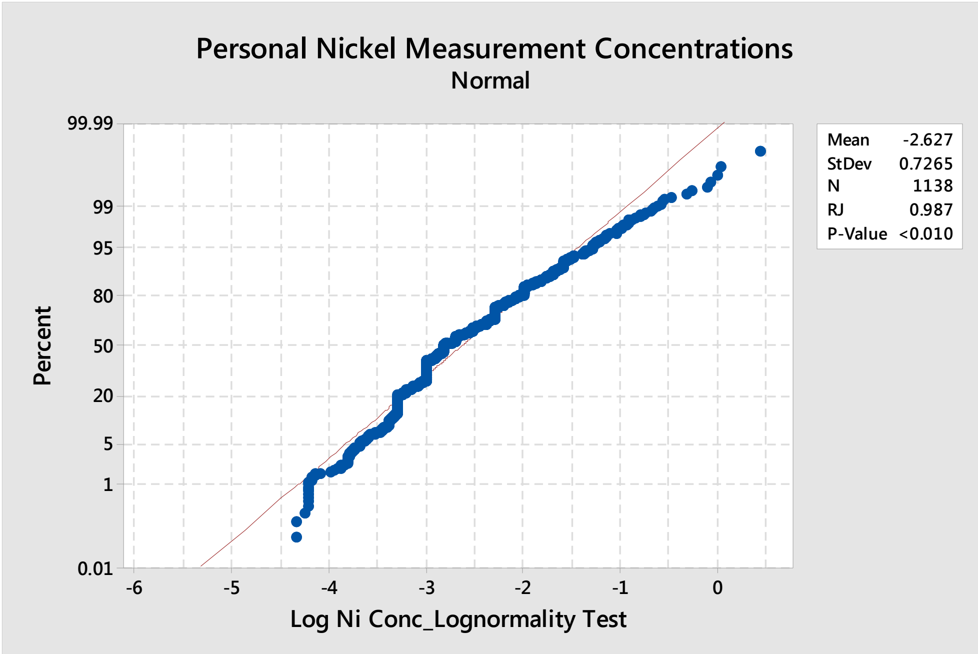

Figure 21. Lognormality graph of personal nickel measurements.

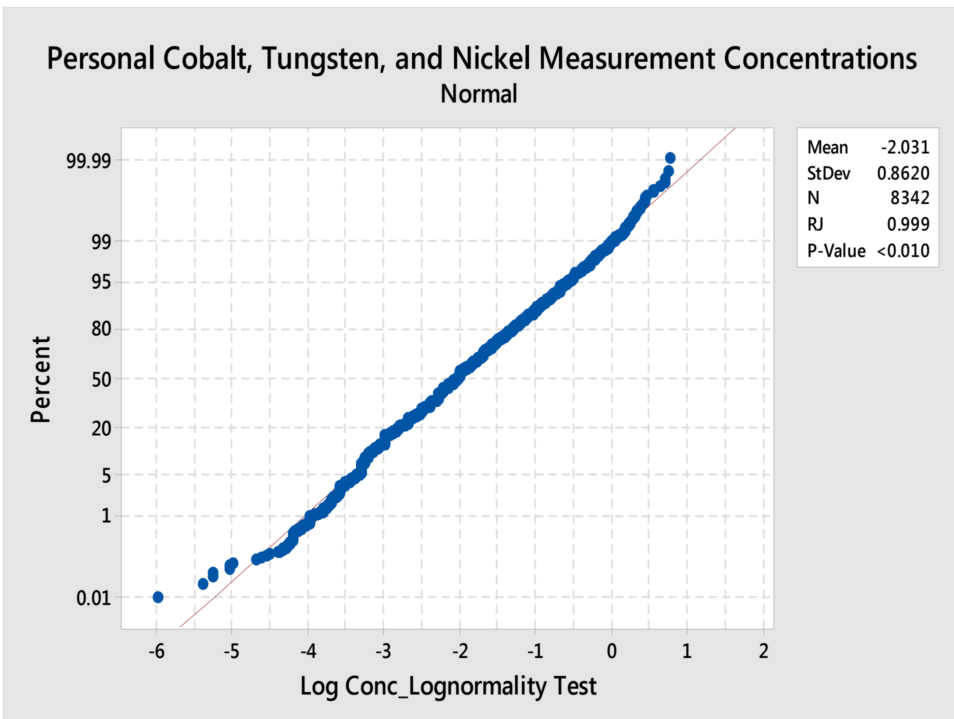

Figure 22. Lognormality graph of personal cobalt, tungsten, and nickel measurements.

APPENDIX L

TABLE X

PERSONAL INDUSTRIAL HYGIENE MEASUREMENTS BY AGENT AND COUNTRY

Agent	**Country**	**Time Period Covered**	**N**	**Percent Censored (%)**
Cobalt (total aerosol)	US	1980 - 2012	3,854	14
Cobalt (inhalable fraction)	US	2013	34	38
Tungsten (total aerosol)	US	1986 - 2010	258	10
Tungsten (inhalable fraction)	US	—	0	—
Nickel (total aerosol)	US	1985 - 2012	653	56
Nickel (inhalable fraction)	US	—	0	—
Cobalt (total aerosol)	AT	1998 - 2012	39	5
Cobalt (inhalable fraction)	AT	—	0	0
Tungsten (total aerosol)	AT	2006 - 2012	35	0
Tungsten (inhalable fraction)	AT	—	0	0
Nickel (total aerosol)	AT	—	0	—
Nickel (inhalable fraction)	AT	—	0	—
Cobalt (total aerosol)	GE	1982 - 2012	168	17
Cobalt (inhalable fraction)	GE	1986 - 1994	22	5
Tungsten (total aerosol)	GE	1998 - 2012	80	16
Tungsten (inhalable fraction)	GE	—	0	—
Nickel (total aerosol)	GE	1983 - 2012	55	71
Nickel (inhalable fraction)	GE	—	0	—
Cobalt (total aerosol)	SE	1965 - 2012	1,161	5
Cobalt (inhalable fraction)	SE	2010 - 2012	50	0
Tungsten (total aerosol)	SE	1983 - 2011	341	1
Tungsten (inhalable fraction)	SE	—	0	—
Nickel (total aerosol)	SE	1978 - 2011	314	35
Nickel (inhalable fraction)	SE	—	0	—
Cobalt (total aerosol)	UK	1988 - 2002	34	18
Cobalt (inhalable fraction)	UK	1988 - 2013	813	20
Tungsten (total aerosol)	UK	1988	22	0
Tungsten (inhalable fraction)	UK	2004 - 2013	287	10
Nickel (total aerosol)	UK	—	0	—
Nickel (inhalable fraction)	UK	2004 - 2013	116	88

APPENDIX L (continued)

TABLE X (continued)

PERSONAL INDUSTRIAL HYGIENE MEASUREMENTS BY AGENT AND COUNTRY

Agent	Country	Time Period Covered	N	Percent Censored (%)
Cobalt[a]	Pooled[b]	1965 - 2013	6,175	13
Tungsten[a]	Pooled	1983 - 2013	1,023	7
Nickel[a]	Pooled	1978 - 2013	1,138	54

[a]Total aerosol and inhalable fraction combined.

[b]All countries combined.

APPENDIX M

TABLE XI

PERSONAL COBALT MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Background and Support Operations					
00	Background	17	35	US, SE	1974-2012	1	0	6	17
01	Laboratory/Research & Development	127	33	US, SE, UK	1978-2012	20	35	21	0
02-03	Supervisory, Engineering	11	9	US, SE, UK	2002-2010	3	33	4	0
04	Trades	228	13	US, GE, SE, UK	1980-2013	98	14	13	0
05	Material handling	34	9	US, UK	1984-2012	5	0	0	—
06	Assembly[c]	1	100	US	2011	0	—	0	—
07	Mark/pack	15	20	US, UK	1985-2007	7	14	0	—
08	Inspection	55	33	US, SE, UK	1978-2010	3	33	19	47
				General Production Operations					
09	Powder weigh	330	4	US, GE, SE, UK	1978-2013	37	11	139	4
10	Powder mix	35	0	US, SE, UK	1986-2012	2	0	3	0
11-12	Powder sieve, Pelletize	175	2	US, SE, UK	1978-2012	7	0	28	4
13	Powder package	72	6	US, GE, SE	1978-2011	0	—	16	25
14	Press set-up	101	8	US, SE, UK	1984-2013	26	15	3	0
15	Press	1233	7	US, AT, GE, SE, UK	1974-2013	129	9	284	6
16	Shape	542	6	US, AT, GE, SE, UK	1970-2012	89	15	69	0
17	Extrude	35	0	US, GE, UK	1988-2012	14	0	0	—

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

APPENDIX M (continued)

TABLE XI (continued)

PERSONAL COBALT MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				General Production Operations					
18	Cold isostatic press	114	2	US, GE, SE, UK	1970-2012	34	3	5	0
19	Furnace set-up	26	4	US	1980-2008	0	—	0	—
20	Furnace	186	22	US, GE, SE, UK	1986-2013	35	60	16	0
21	Computer numerical control operation	101	34	US, GE, UK	1983-2012	11	18	0	—
22	Hone	98	49	US, SE, UK	1984-2012	3	67	1	0
23	Grind	943	27	US, GE, SE, UK	1965-2013	108	47	131	10
24	Slow moving operations	19	11	US, SE	1988 - 2012	2	0	7	14
25	Electro-discharge machining	7	71	US	1999 - 2009	0	—	0	—
26	Blast	74	47	US, GE, SE, UK	1982-2012	15	67	13	0
27	Coat	33	30	US, GE, SE, UK	1974-2012	5	80	19	0
				Tungsten Carbide Powder Production Operations					
28-30	Ball mill, Fitz mill, Attritor	226	4	US, SE, GE, UK	1978-2013	47	15	20	10
31	Spray dry	293	5	US, SE, UK	1982-2012	81	11	71	1
32	Mill and spray dry	154	1	US, SE	1978-2010	0	—	6	0
33	Ammonium-paratungstate process[c]	0	—	—	—	0	—	0	—

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

APPENDIX M (continued)

TABLE XI (continued)

PERSONAL COBALT MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Tungsten Carbide Powder Production Operations					
34	Thermit process	18	22	US	1992-2010	0	—	0	—
52	WC powder production unspecified[c]	1	0	SE	2005	0	—	0	—
				Additional Operations					
35	Weld	14	7	US	2001-2012	0	—	0	—
36	Braze	41	78	US	195-2012	0	—	0	—
37, 65	Rapid omni-directional compaction, Foundry	9	33	US	2005-2010	0	—	0	—
39	Powder room operations	272	16	US, AT, SE, UK	1990-2013	61	16	1	0
40-41, 63	Ceramic processes[c,d]	1	100	GE	2012	0	—	0	—
42	Dry grind	21	24	US, GE	1982-2010	0	—	0	—
43	Recycling	108	0	US, UK	1988-2010	29	0	0	—
44	Mechanical production	30	27	US	1990-2012	0	—	0	—
45	Graphite service	16	13	US, AT, GE	1980-2008	0	—	0	—
46	Heavy metal powder production	211	2	GE, SE	1978-2012	12	0	194	1
47	Medical engineering[c]	0	—	—	—	0	—	0	—

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Includes ceramic grinding, ceramic weighing, and other ceramic operations.

APPENDIX M (continued)

TABLE XI (continued)

PERSONAL COBALT MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Additional Operations					
50	Press/form/sinter	37	0	SE	1981-2012	4	0	33	0
53	W production[c]	0	—	—	—	0	—	0	—
55	WC parts production unspecified	36	8	US, SE, UK	1984-2012	4	0	9	0
56-61	Rolls processes[e]	34	0	SE	1978-2011	0	—	34	0
62	Hydrogen gas production[c]	0	—	—	—	0	—	0	—
64	WC powder/parts production unspecified	27	7	US, UK	1988-2009	5	20	0	—
66	Tube milling	14	14	US	1992-2010	0	—	0	—
				Other					
75	Blue collar worker[c]	0	—	—	—	0	—	0	—
38, 48-49, 85	Out of plant[f]	N/A[g]	N/A[g]	N/A[g]	N/A[g]	N/A[g]	N/A[g]	N/A[g]	N/A[g]

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Includes ceramic grinding, ceramic weighing, and other ceramic operations.

[e]Includes unspecified rolls operations and rolls pressing, shaping, sintering, grinding, and inspection.

[f]Includes mine, metals (white collar), metals (blue collar), and leave/time spent out of plant.

[g]Not applicable; exposures outside of plant would not be measured.

APPENDIX N

TABLE XII

PERSONAL TUNGSTEN MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Background and Support Operations					
00	Background[c]	1	0	SE	2005	0	—	1	0
01	Laboratory/Research & Development	24	21	US, UK	1993 - 2010	17	24	0	—
02-03	Supervisory, Engineering	4	0	SE	2008 - 2010	0	—	4	0
04	Trades	62	13	US, SE, UK	1988 - 2011	52	13	2	0
05-08	Material handling, assembly, mark/pack, inspection	10	10	US, UK, SE	1988 - 2011	0	—	8	0
				General Production Operations					
09	Powder weigh	64	0	US, GE, SE, UK	1983 - 2011	20	0	27	0
10	Powder mix	6	0	US, UK	1999 - 2006	2	0	0	—
11-12	Powder sieve, Pelletize	27	0	US, SE, UK	1983 - 2001	0	—	15	0
13	Powder package	14	7	US, SE	1998 - 2011	0	—	13	8
14-15	Press set-up, Press	186	3	US, AT, GE, SE, UK	1983 - 2012	19	0	107	1
16	Shape	65	2	US, AT, GE, SE, UK	1990 - 2012	5	0	13	0
17	Extrude	8	0	US, GE	1988 - 2007	3	0	0	—
18	Cold isostatic press	12	0	US, GE, SE	1987 - 2011	0		2	0
19-20	Furnace set-up, Furnace	37	11	US, GE, SE, UK	1986 - 2012	9	33	3	0

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

APPENDIX N (continued)

TABLE XII (continued)

PERSONAL TUNGSTEN MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				General Production Operations					
21	Computer numerical control operation	13	31	US, GE, UK	1999 - 2011	5	20	0	—
22	Hone	8	63	US	1987 - 2006	0	—	0	—
23	Grind	78	21	US, GE, SE, UK	1983 - 2013	14	64	18	0
24	Slow moving operations	4	0	US, SE	1989 - 1999	0	—	1	0
25	Electro-discharge machining[c]	1	100	US	2006	—	—	—	—
26	Blast[c]	2	50	GE, UK	1998 - 2009	1	0	0	—
27	Coat	13	15	GE, SE	2008 - 2012	0	—	11	0
				Tungsten Carbide Powder Production Operations					
28-30	Ball mill, Fitz mill, Attritor	33	0	US, GE, SE, UK	1987 - 2012	23	0	2	0
31	Spray dry	95	2	US, SE, UK	1987 - 2009	53	4	39	0
32	Mill and spray dry	19	0	US, SE	1986 - 2010	0	—	0	—
33	Ammonium paratungstate process[c]	0	—	—	—	0	—	0	—
34	Thermit process	27	0	US	1994 - 2010	0	—	0	—
52	WC powder production unspecified[c]	0	—	—	—	0	—	0	—

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

APPENDIX N (continued)

TABLE XII (continued)

PERSONAL TUNGSTEN MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Additional Operations					
35	Weld[c]	0	—	—	—	0	—	0	—
36	Braze[d]	7	100	US	1998 - 2006	0	—	0	—
37, 65	Rapid omni-directional compaction, Foundry	0	—	—	—	0	—	0	—
39	Powder room operations	52	2	US, UK	1990 - 2009	40	3	0	—
40-41, 63	Ceramic processes[c,e]	1	100	GE	2012	0	—	0	—
42	Dry grind	7	14	US, GE	1999 - 2007	0	—	0	—
43	Recycling	54	2	US, UK	1988 - 2010	24	4	0	—
44	Mechanical production[c]	0	—	—	—	0	—	0	—
45	Graphite service[c]	2	50	GE	1999 - 2003	0	—	0	—
46	Heavy metal powder production	70	0	GE, SE	1994 - 2012	0	—	66	0
47	Medical engineering[c]	0	—	—	—	0	—	0	—
50	Press/form/sinter[f]	1	0	SE	1994	0	—	1	0
53	W production[c]	0	—	—	—	0	—	0	—

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Due to high censoring and limited measurements, exposure interval assigned by professional judgment.

[e]Includes ceramic grinding, ceramic weighing, and other ceramic operations.

[f]Used 122 Swedish measurements from job classes 15, 16, 20, and 50 combined to calculate exposure interval.

APPENDIX N (continued)

TABLE XII (continued)

PERSONAL TUNGSTEN MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Additional Operations					
55	WC parts production unspecified	7	0	US, SE	1994 - 2002	0		2	0
56-61	Rolls processes[g]	5	0	SE	1994 - 2011	0	—	5	0
62	Hydrogen gas production[c]	0	—	—	—	0	—	0	—
64	WC powder/parts production unspecified[c]	1	0	UK	1988	0	—	0	—
66	Tube milling	3	0	US	2006 - 2010	0	—	0	—
				Other					
75	Blue collar worker[c]	0	—	—	—	0	—	0	—
38, 48-49 85	Out of plant[h]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Due to high censoring and limited measurements, exposure interval assigned by professional judgment.

[e]Includes ceramic grinding, ceramic weighing, and other ceramic operations.

[f]Used 122 Swedish measurements from job classes 15, 16, 20, and 50 combined to calculate exposure interval.

[g]Includes unspecified rolls operations and rolls pressing, shaping, sintering, grinding, and inspection.

[h]Includes mine, metals (white collar), metals (blue collar), and leave/time spent out of plant.

[i]Not applicable; exposures outside of plant would not be measured.

APPENDIX O

TABLE XIII

PERSONAL NICKEL MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Background and Support Operations					
00	Background[c]	1	0	SE	1986	0	—	1	0
01	Laboratory/Research & Development	21	62	US, SE	1982 - 2010	0	—	5	20
02-03	Supervisory, Engineering[c]	1	100	UK	2005	1	100	0	—
04	Trades	18	50	US, GE, SE, UK	1983 - 2011	2	50	1	0
05-08	Material handling, assembly, mark/pack, inspection	6	67	US, UK	1988 - 2011	1	100	0	—
				General Production Operations					
09	Powder weigh	112	29	US, GE, SE	1979 - 2011	1	0	81	25
10	Powder mix	9	78	US	1987 - 1999	0	—	0	—
11-12	Powder sieve, Pelletize	62	19	US, SE	1978 - 2005	0	—	20	10
13	Powder package	15	60	US, SE	1978 - 2008	0	—	1	0
14-15	Press set-up, Press	168	71	US, GE, SE, UK	1978 - 2012	32	94	56	54
16	Shape	108	61	US, GE, SE, UK	1986 - 2012	20	90	10	0
17	Extrude[d]	12	100	US	1995 - 2003	0	—	1	0
18	Cold isostatic press	19	53	US, GE, SE	1987 - 2011	0	—	1	100
19-20	Furnace set-up, Furnace	52	38	US, SE, UK	1987 - 2012	11	82	3	33

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Due to high censoring and limited measurements, exposure interval assigned by professional judgment.

APPENDIX O (continued)

TABLE XIII (continued)

PERSONAL NICKEL MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	**Job Class Group[a]**	**N**	**Percent Censored (%)**	**Countries Represented in Measurements**	**Time Period Covered by Measurements**	**N (Inhalable Fraction)**	**Percent Censored Inhalable (%)**	**N (OFC[b])**	**Percent Censored OFC (%)**
				General Production Operations					
21-23	Computer numerical control operation, Hone, Grind	214	69	US, GE, SE, UK	1978 - 2013	34	91	46	35
24	Slow moving operations	8	38	US, SE	1988 - 2006	0	—	3	33
25	Electro-discharge machining[c]	0	—	—	—	0	—	0	—
26	Blast[d]	11	82	US, UK	2004 - 2007	9	78	0	—
27	Coat[d]	7	100	US, GE, UK	2001 - 2012	3	100	0	—
				Tungsten Carbide Powder Production Operations					
28-32	Ball mill, Fitz mill, Attritor, Spray dry, Mill and spray dry	134	59	US, GE, SE, UK	1978 - 2012	1	0	46	63
33	Ammonium paratungstate process[c]	0	—	—	—	0	—	0	—
34	Thermit process	3	0	US	2008 - 2010	0	—	0	—
52	WC powder production unspecified[c]	0	—	—	—	0	—	0	—

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Due to high censoring and limited measurements, exposure interval assigned by professional judgment.

APPENDIX O (continued)

TABLE XIII (continued)

PERSONAL NICKEL MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Additional Operations					
35	Weld	17	12	US	2000 - 2008	0	—	0	—
36	Braze	31	87	US	1995 - 2010	0	—	0	—
37, 65	Rapid omni-directional compaction, Foundry	11	18	US	1999 - 2010	0	—	0	—
39	Powder room operations	11	36	US	1990 - 2011	0	—	0	—
40-41, 63	Ceramic processes[c,e]	1	100	GE	2012	0	—	0	—
42	Dry grind	5	80	US, GE	1995 - 2007	0	—	0	—
43	Recycling	6	0	US	1998 - 2010	0	—	0	—
44	Mechanical production	19	16	US	1985 - 2010	0	—	0	—
45	Graphite service[c]	2	100	US	1990- 1998	0	—	0	—
46	Heavy metal powder production	28	18	GE, SE	1985 - 2012	0	—	20	25
47	Medical engineering[c]	0	—	—	—	0	—	0	—
50	Press/form/sinter[f]	1	0	SE	1994	0	—	1	0
53	W production[c]	0	—	—	—	0	—	0	—

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Due to high censoring and limited measurements, exposure interval assigned by professional judgment.

[e]Includes ceramic grinding, ceramic weighing, and other ceramic operations.

[f]Used 70 Swedish measurements from job classes 15, 16, 20, and 50 combined to calculate exposure interval.

APPENDIX O (continued)

TABLE XIII (continued)

PERSONAL NICKEL MEASUREMENTS MEETING INCLUSION CRITERIA BY JOB CLASS

Job Class Number[a]	Job Class Group[a]	N	Percent Censored (%)	Countries Represented in Measurements	Time Period Covered by Measurements	N (Inhalable Fraction)	Percent Censored Inhalable (%)	N (OFC[b])	Percent Censored OFC (%)
				Additional Operations					
55	WC parts production unspecified	6	33	US, SE	1997 - 2012	0	—	1	0
56-61	Rolls processes[g]	18	11	SE	1978 - 2005	0	—	18	11
62	Hydrogen gas production[c]	0	—	—	—	0	—	0	—
64	WC powder/parts production unspecified[c]	0	—	—	—	0	—	0	—
66	Tube milling[c]	1	0	US	2010	0	—	0	—
				Other					
75	Blue collar worker[c]	0	—	—	—	0	—	0	—
38, 48-49, 85	Out of plant[h]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]	N/A[i]

[a]Job classes where Co data was combined for analyses are shown in same row.

[b]Open-face cassette; used in Sweden only.

[c]Due to lack of IH measurements, exposure interval assigned by professional judgment.

[d]Due to high censoring and limited measurements, exposure interval assigned by professional judgment.

[e]Includes ceramic grinding, ceramic weighing, and other ceramic operations.

[f]Used 70 Swedish measurements from job classes 15, 16, 20, and 50 combined to calculate exposure interval.

[g]Includes unspecified rolls operations and rolls pressing, shaping, sintering, grinding, and inspection.

[h]Includes mine, metals (white collar), metals (blue collar), and leave/time spent out of plant.

[i]Not applicable; exposures outside of plant would not be measured.

APPENDIX P: Qualitative Factor Analysis

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Country	5	1, 2, 3, 4, 5

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Country	4	159.3	39.8347	58.73	0.000
Error	8331	5650.9	0.6783		
Total	8335	5810.2			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.823587	2.74%	2.70%	2.63%

Means

Country	N	Mean	StDev	95% CI
1	74	-1.1876	0.7489	(-1.3753, -0.9999)
2	325	-1.7323	0.7855	(-1.8219, -1.6428)
3	1866	-1.9761	0.8397	(-2.0135, -1.9388)
4	1272	-1.8166	0.8815	(-1.8618, -1.7713)
5	4799	-2.0952	0.8048	(-2.1185, -2.0719)

Pooled StDev = 0.823587

Figure 23A.

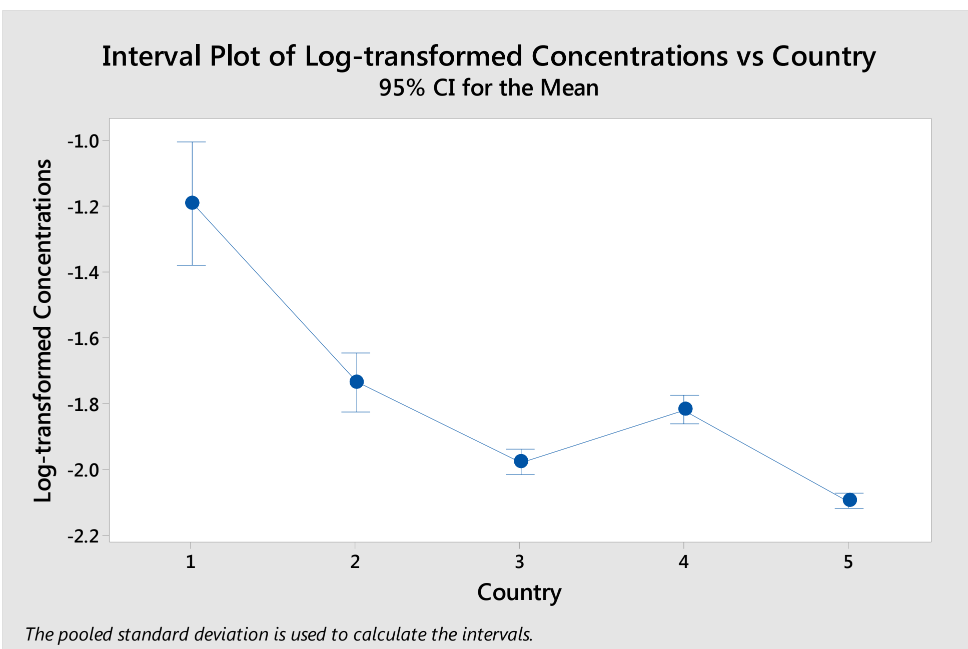

Figure 23B.

Figure 23. Statistical analysis output and interval plot of agent concentrations versus country.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	$\alpha = 0.05$

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Company	3	1, 2, 3

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Company	2	69.87	34.9352	50.71	0.000
Error	8333	5740.35	0.6889		
Total	8335	5810.22			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.829982	1.20%	1.18%	1.13%

Means

Company	N	Mean	StDev	95% CI
1	74	-1.1876	0.7489	(-1.3767, -0.9985)
2	3191	-1.9489	0.8789	(-1.9777, -1.9201)
3	5071	-2.0503	0.7988	(-2.0731, -2.0274)

Pooled StDev = 0.829982

Figure 24A.

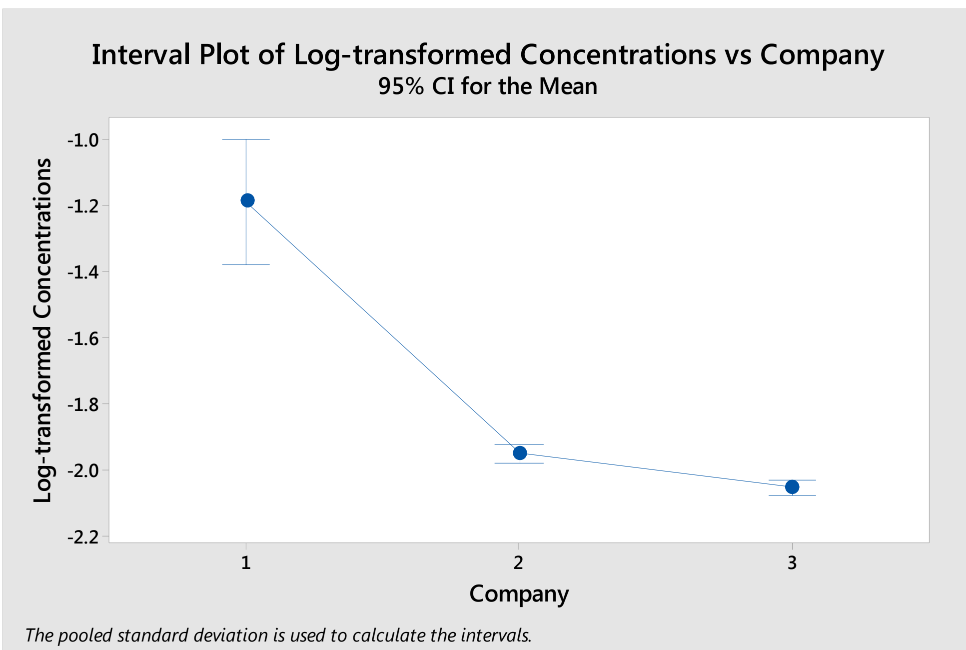

Figure 24B

Figure 24. Statistical analysis output and interval plot of agent concentrations versus company.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Plant	21	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Plant	20	1284	64.1908	117.92	0.000
Error	8315	4526	0.5444		
Total	8335	5810			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.737812	22.10%	21.91%	21.67%

Means

Plant	N	Mean	StDev	95% CI
1	50	-2.9173	0.5456	(-3.1219, -2.7128)
2	256	-2.2835	0.7405	(-2.3739, -2.1931)
3	421	-1.2906	0.7977	(-1.3611, -1.2201)
4	309	-1.7179	1.0181	(-1.8002, -1.6356)
5	227	-1.6675	0.7038	(-1.7635, -1.5715)
6	293	-2.7589	0.7215	(-2.8434, -2.6744)
7	430	-2.4109	0.7161	(-2.4807, -2.3412)
8	18	-2.508	0.671	(-2.849, -2.168)
9	52	-2.402	0.946	(-2.603, -2.202)
10	1092	-2.0517	0.6087	(-2.0955, -2.0079)
12	841	-2.5664	0.5172	(-2.6163, -2.5166)
13	810	-1.7996	0.6670	(-1.8504, -1.7488)
15	74	-1.1876	0.7489	(-1.3557, -1.0195)
16	81	-1.9814	0.6361	(-2.1421, -1.8207)
17	54	-1.803	1.023	(-1.999, -1.606)
18	190	-1.6061	0.7410	(-1.7111, -1.5012)
19	415	-2.1590	1.0019	(-2.2300, -2.0880)
20	478	-2.2601	0.6848	(-2.3262, -2.1939)
21	973	-1.7586	0.7706	(-1.8050, -1.7123)
22	934	-1.5920	0.8550	(-1.6393, -1.5447)
23	338	-2.4372	0.6168	(-2.5158, -2.3585)

Pooled StDev = 0.737812

Figure 25A.

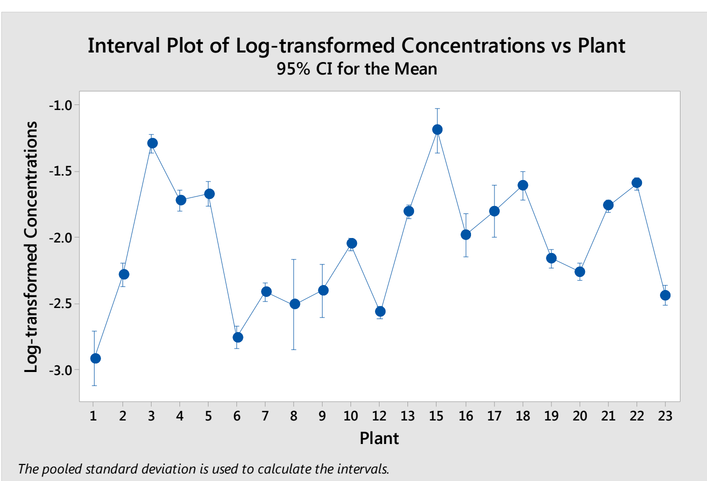

Figure 25B.

Figure 25. Statistical analysis output and interval plot of agent concentrations versus plant.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Plant Type	3	1, 2, 3

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Plant Type	2	637.7	318.846	513.66	0.000
Error	8333	5172.5	0.621		
Total	8335	5810.2			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.787863	10.98%	10.95%	10.91%

Means

Plant Type	N	Mean	StDev	95% CI
1	1437	-2.4839	0.7242	(-2.5246, -2.4431)
2	3540	-2.0846	0.7431	(-2.1105, -2.0586)
3	3359	-1.7133	0.8568	(-1.7400, -1.6867)

Pooled StDev = 0.787863

Figure 26A.

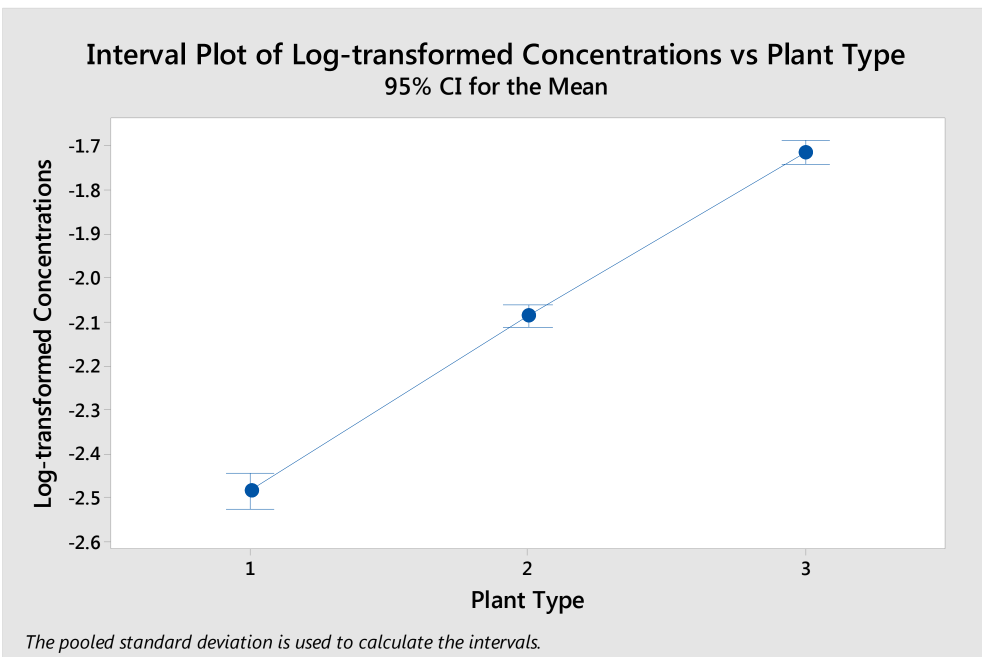

Figure 26B.

Figure 26. Statistical analysis output and interval plot of agent concentrations versus plant type.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Age of Facility	2	1, 2

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Age of Facility	1	85.55	85.5452	124.54	0.000
Error	8334	5724.68	0.6869		
Total	8335	5810.22			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.828798	1.47%	1.46%	1.42%

Means

Age of Facility	N	Mean	StDev	95% CI
1	5424	-1.9296	0.7949	(-1.9516, -1.9075)
2	2912	-2.1421	0.8885	(-2.1722, -2.1120)

Pooled StDev = 0.828798

Figure 27A.

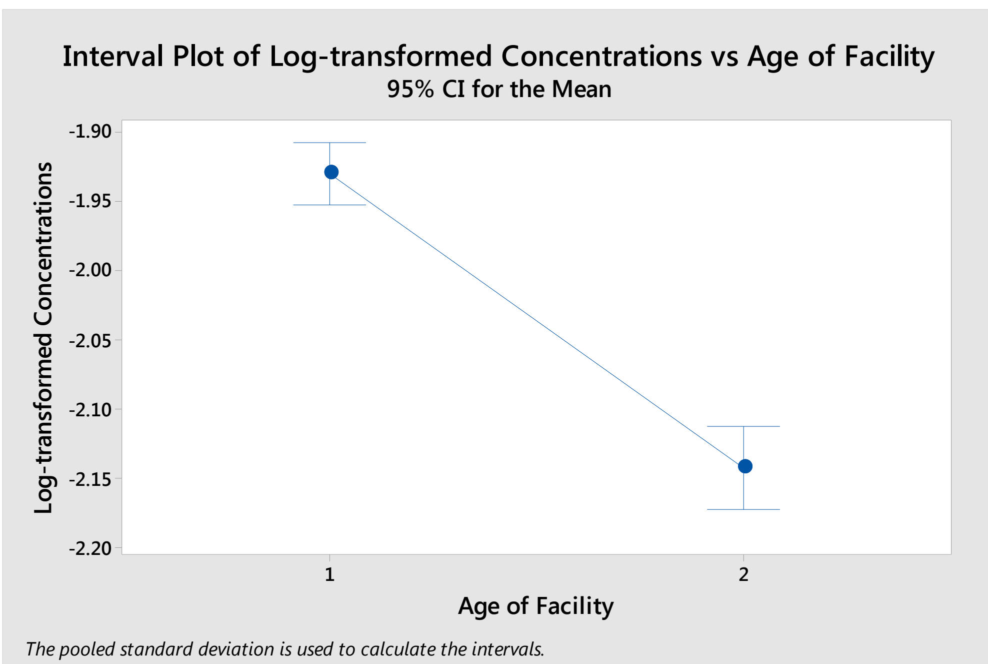

Figure 27B.

Figure 27. Statistical analysis output and interval plot of agent concentrations versus age of facility.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Job Class Category	3	1, 2, 3

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Job Class Category	2	625.0	312.479	502.17	0.000
Error	8333	5185.3	0.622		
Total	8335	5810.2			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.788833	10.76%	10.73%	10.69%

Means

Job Class Category	N	Mean	StDev	95% CI
1	636	-2.2292	0.8721	(-2.2905, -2.1679)
2	5104	-2.1826	0.7617	(-2.2043, -2.1610)
3	2596	-1.5971	0.8193	(-1.6274, -1.5667)

Pooled StDev = 0.788833

Figure 28A.

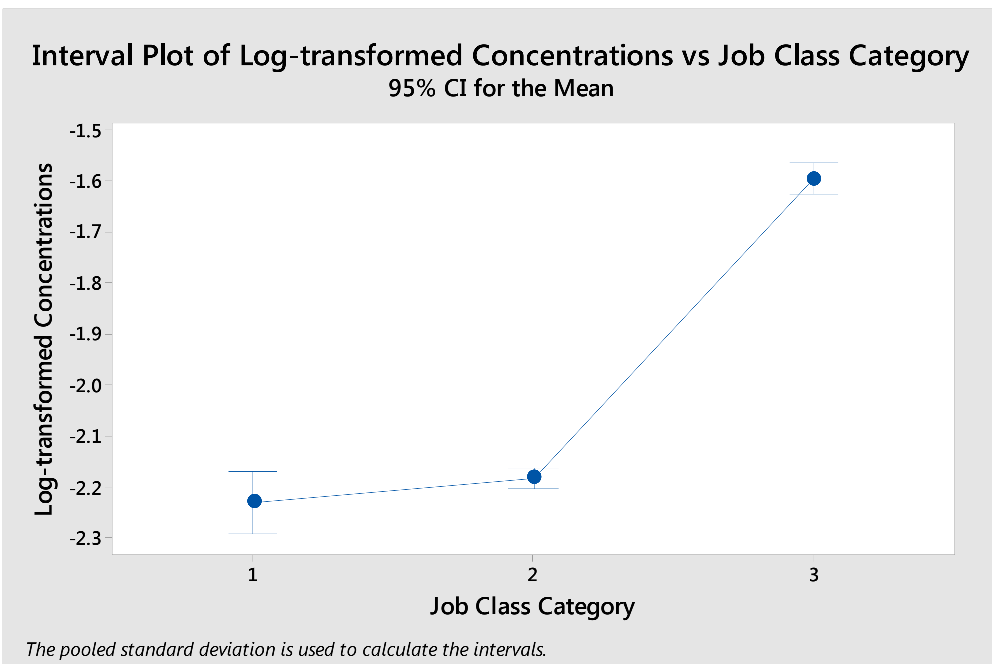

Figure 28B.

Figure 28. Statistical analysis output and interval plot of agent concentrations versus major job class category.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Production Phase	3	1, 2, 3

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Production Phase	2	540.3	270.171	427.21	0.000
Error	8333	5269.9	0.632		
Total	8335	5810.2			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.795243	9.30%	9.28%	9.23%

Means

Production Phase	N	Mean	StDev	95% CI
1	708	-2.2681	0.8670	(-2.3267, -2.2095)
2	1966	-2.4078	0.8211	(-2.4429, -2.3726)
3	5662	-1.8305	0.7765	(-1.8512, -1.8098)

Pooled StDev = 0.795243

Figure 29A.

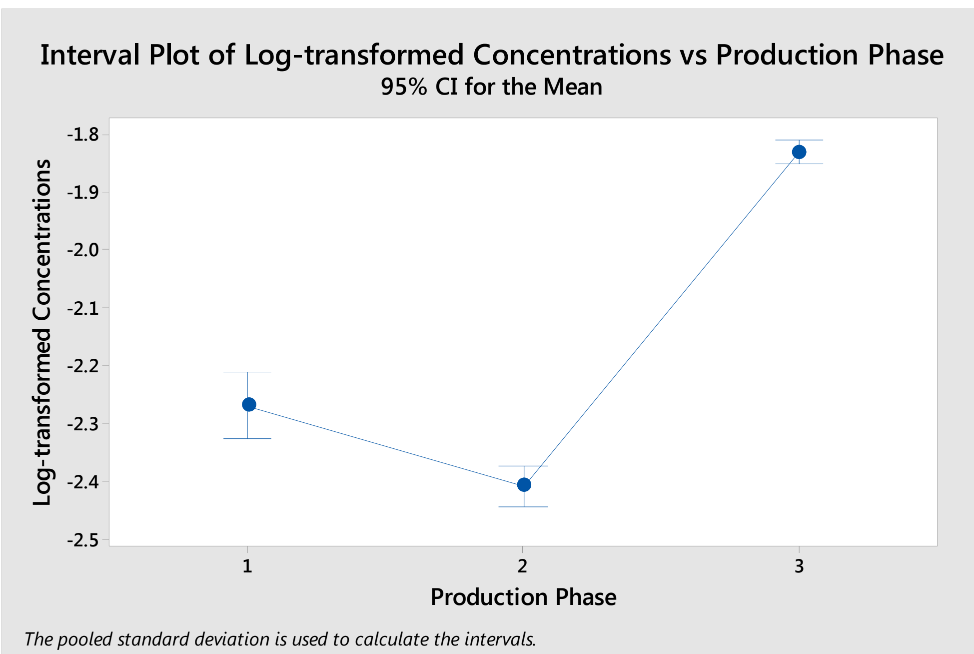

Figure 29B.

Figure 29. Statistical analysis output and interval plot of agent concentrations versus production phase.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Particulate Fraction	2	1, 2

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Particulate Fraction	1	18.15	18.1460	26.11	0.000
Error	8334	5792.08	0.6950		
Total	8335	5810.22			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.833663	0.31%	0.30%	0.26%

Means

Particulate Fraction	N	Mean	StDev	95% CI
1	7014	-2.02407	0.82702	(-2.04358, -2.00456)
2	1322	-1.8963	0.8681	(-1.9413, -1.8514)

Pooled StDev = 0.833663

Figure 30A.

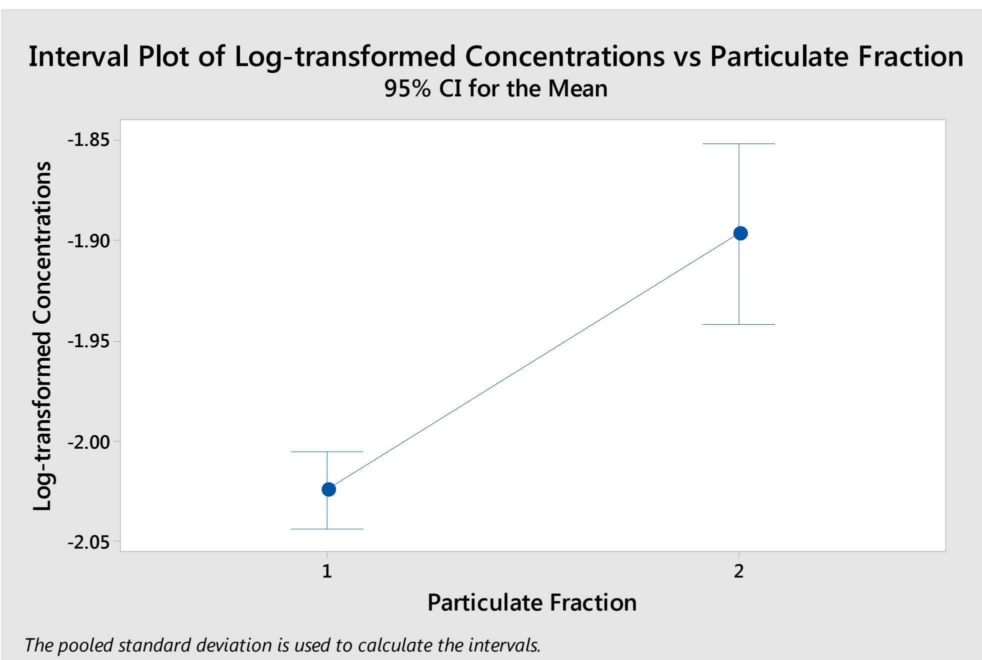

Figure 30B.

Figure 30. Statistical analysis output and interval plot of agent concentrations versus particulate fraction.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
Analysis Period	3	1, 2, 3

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Analysis Period	2	143.4	71.6966	105.43	0.000
Error	8333	5666.8	0.6800		
Total	8335	5810.2			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.824650	2.47%	2.44%	2.40%

Means

Analysis Period	N	Mean	StDev	95% CI
1	1480	-1.8219	0.7823	(-1.8639, -1.7799)
2	2059	-1.8743	0.8000	(-1.9099, -1.8386)
3	4797	-2.1155	0.8475	(-2.1389, -2.0922)

Pooled StDev = 0.824650

Figure 31A.

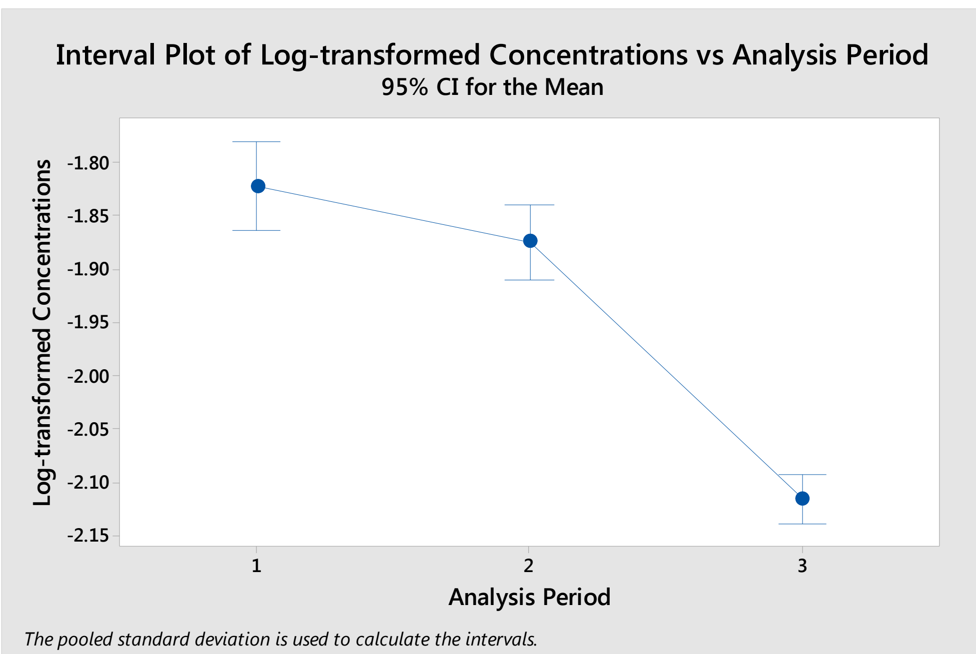

Figure 31B.

Figure 31. Statistical analysis output and interval plot of agent concentrations versus analysis period.

APPENDIX P: Qualitative Factor Analysis (continued)

Method

Null hypothesis	All means are equal
Alternative hypothesis	At least one mean is different
Significance level	α = 0.05

Equal variances were assumed for the analysis.

Factor Information

Factor	Levels	Values
TLV Time Period	6	1, 2, 3, 4, 5, 6

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
TLV Time Period	5	1352	270.311	505.02	0.000
Error	8330	4459	0.535		
Total	8335	5810			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.731611	23.26%	23.22%	23.16%

Means

TLV Time Period	N	Mean	StDev	95% CI
1	548	-1.7058	0.6423	(-1.7671, -1.6445)
2	974	-1.7307	0.7461	(-1.7767, -1.6848)
3	4653	-2.1545	0.7352	(-2.1755, -2.1335)
4	1023	-1.1362	0.7994	(-1.1810, -1.0913)
5	495	-2.3890	0.7063	(-2.4535, -2.3246)
6	643	-2.6650	0.6574	(-2.7215, -2.6084)

Pooled StDev = 0.731611

Figure 32A.

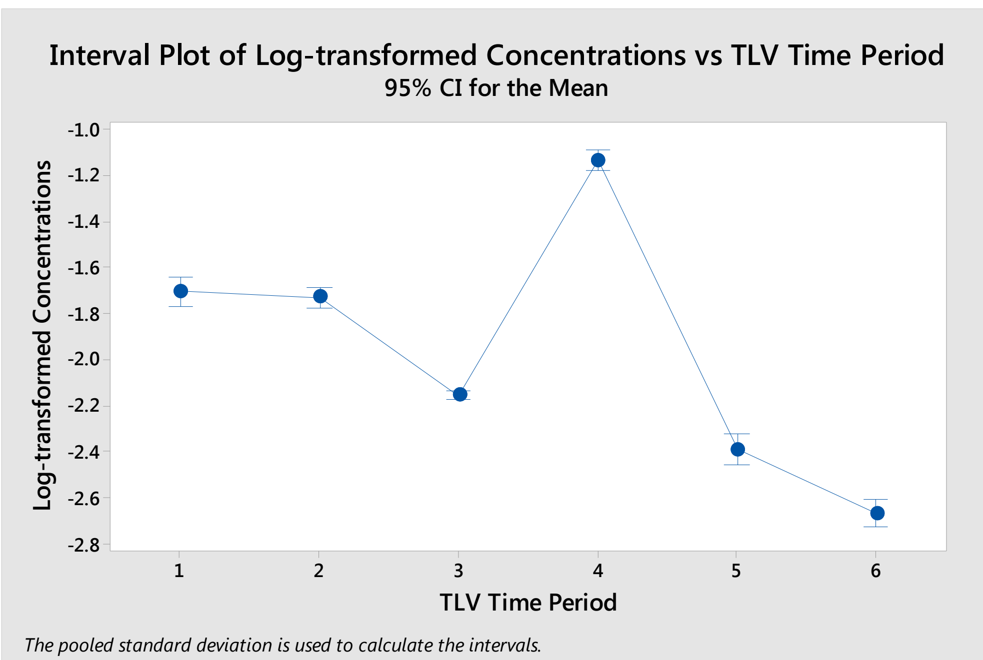

Figure 32B.

Figure 32. Statistical analysis output and interval plot of agent concentrations versus threshold limit value (TLV) time period.

VITA

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	Marsh, G.M., Youk, A.O., Buchanich, J.M., Xu, H., Downing, S., Kennedy, K.J., Esmen, N.A., Hancock, R.P., Lacey, S.E., and Fleissner, M.L.: Long-term health experience of jet engine manufacturing workers: VI: Incidence of malignant central nervous system neoplasms in relation to estimated workplace exposures. <u>J. Occup.Env. Med.</u> 55:654-675, 2013.

VITA (continued)

Marsh, G.M., Youk, A.O., Buchanich, J.M., Downing, S., Kennedy, K.J., Esmen, N.A., Hancock, R.P., Lacey, S.E., Pierce, J.S., and Fleissner, M.L.: Long-term health experience of jet engine manufacturing workers: VIII. Glioblastoma incidence in relation to workplace experiences with parts and processes. J. Occup.Env. Med. 55:690-708, 2013.

Youk, A.O., Marsh, G.M., Buchanich, J.M., Downing, S., Kennedy, K.J., Esmen, N.A., Hancock, R.P., and Lacey, S.E.: Long-term health experience of jet engine manufacturing workers: IX. Further investigation of general mortality patterns in relation to workplace exposures. J. Occup.Env. Med. 55:709-721, 2013.

Marsh, G.M., Buchanich, J.M., Youk, A.O., Downing, S., Esmen, N.A., Kennedy, K.J., Hancock, R.P., Lacey, S.E., Fleissner, M.L., Lieberman, F.S.: Long-term health experience of jet engine manufacturing workers: Results from a 12-year exploratory investigation. J. Occup.Env. Med. 55:652-653, 2013.

Buchanich, J.M., Youk, A.O., Marsh, G.M., Lacey, S.E., Kennedy, K.J., Hancock, R.H., Esmen, N.E., Lieberman, F.S., and Fleissner, M.L.: Long-term health experience of jet engine manufacturing workers: V. Issues with the analysis of non-malignant central nervous system neoplasms. J. Registry Manag. 38:115-119, 2011.

Buchanich, J.M., Youk, A.O., Marsh, G.M., Kennedy, K.J., Esmen, N.E., Lacey, S.E., Hancock, R.P., Cunningham, M.A., Lieberman, F.S., and Fleissner, M.L.: Long-term health experience of jet engine manufacturing workers: IV. A comparison of central nervous system cancer ascertainment using mortality and incidence data. Ann. Epidemiol. 20:759-765, 2010.

Marsh, G.M., Buchanich, J.M., Youk, A.O., Cunningham, M.A., Lieberman, F.S., Kennedy, K.J., Lacey, S.E., Hancock, R.P., Esmen, N.A., and Fleissner, M.L.: Long-term health experience of jet engine manufacturing workers: III. Incidence of malignant central nervous system neoplasms. Neuroepidemiology 35:123-141, 2010.

Buchanich, J.M., Youk, A.O., Marsh, G.M., Bornemann, Z., Lacey, S.E., Kennedy, K.J., Hancock, R.P., Esmen, N.A., and Lieberman, F.S. Methodological issues in a retrospective cancer incidence study. Am. J. Epidemiol. 170:112-119, 2009.

VITA (continued)

Marsh, G.M., Buchanich, J.B., Youk, A.O., Cunningham, M.A., Lieberman, F.S., Kennedy, K.J., Lacey, S.E., Hancock, R.P., and Esmen, N.A.: Long-term health experience of jet engine manufacturing workers: I. Mortality from central nervous system neoplasms. J. Occup. Env. Med. 50:1099-1116, 2008.

Marsh, G.M., Buchanich, J.M., Youk, A.O., Cunningham, M.A., Lieberman, F.S., Kennedy, K.J., Lacey, S.E., Hancock, R.P., and Esmen, N.A.: Long-term health experience of jet engine manufacturing workers: II. Total and cause-specific mortality excluding central nervous system neoplasms. J. Occup. Env. Med. 50:1117-1129, 2008.

Lippert, J.F., Lacey, S.E., Kennedy, K.J., Esmen, N.A., Buchanich, J.M., and Marsh, G.M., (2007). Magnetic field exposure in a nondestructive testing operation. Arch. Environ. Occup. Health 62:187-193, 2007.

Esmen, N.A., Kennedy, K.J., Hall, T.A., Phillips, M.L., and Marsh, G.M.: Classification of worker exposures. Chem. Biol. Interact. 166: 245-253, 2007.

Kennedy, K.J.: Occupational Dust Exposure in Ukrainian Coal Miners. Master’s thesis, University of Illinois at Chicago, Chicago, 2002.