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New Opportunities in Exposure Assessment of Occupational Epidemiology: Use of Measurements to Aid Exposure Reconstruction in Population-Based Studies

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Abstract

Purpose of review—Exposure assessment efforts in population-based studies are increasingly incorporating measurements. The published literature was reviewed to identify the measurement sources and the approaches used to incorporate measurements into these efforts.

Recent findings—The variety of occupations and industries in these studies made collecting participant-specific measurements impractical. Thus, the starting point was often the compilation of large databases of measurements from inspections, published literature, and other exposure surveys. These measurements usually represented multiple occupations, industries, and worksites, and spanned multiple decades. Measurements were used both qualitatively and quantitatively, dependent on the coverage and quality of the data. Increasingly, statistical models were used to derive job-, industry-, time period-, and other determinant-specific exposure concentrations.

Summary—Quantitative measurement-based approaches are increasingly replacing expert judgment, which facilitates the development of quantitative exposure-response associations. Evaluations of potential biases in these measurement sources, and their representativeness of typical exposure situations, warrant additional examination.

Keywords

Occupational Exposure; Case-control studies; Expert Judgment; Job-exposure matrices; Population-based cohort studies

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Compliance with Ethics Guidelines

Conflict of Interest

Pamela J. Dopart and Melissa C. Friesen declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

In epidemiologic studies of cancer and other chronic diseases, accurate exposure assessment is vital to identifying occupational risk factors. Yet it remains one of the biggest challenges. The often long latent period between exposure and disease onset requires exposure scientists to develop exposure estimates for the entirety of the subjects' working lives. Advances in exposure assessment in industry-based studies, which usually focus on a limited number of work sites, have been largely made possible through the use of historical work site-specific measurements and study-specific exposure monitoring efforts to fill knowledge gaps. The measurement data are used to estimate quantitative exposure levels that are incorporated into etiologic analyses to quantify exposure-response associations.

In population-based case-control, cohort, and registry-based studies, the large breadth of occupations and industries makes it impractical to collect measurement data from the participants' current and past workplaces. These studies have usually assigned exposure using one of three approaches: 1) general population-level job-exposure matrices (JEMs) that link occupation groups to exposure estimates, 2) job-by-job expert review of occupational questionnaire responses, or 3) expert-based exposure decision rules that link questionnaire responses to exposure estimates [1]. These approaches have traditionally relied on expert judgment to provide estimates of the probability, intensity, and frequency of exposure for the study subjects. The intensity estimates have often been based on the experts' qualitative review of available measurement data. However, an increasing number of studies have been incorporating measurement data more explicitly and directly into their exposure assessment efforts, such as through the use of statistical modelling of available exposure measurements to predict exposure. Here, we review the approaches that have been used to incorporate measurements into these historical exposure reconstruction efforts in population-based studies.

Job-exposure matrices

Population-level (generic) JEMs are often used to obtain exposure estimates in population-based studies, in part because their use is time- and cost-efficient and because it is usually the only assessment approach available when limited occupational information is collected [1, 2]. These JEMs link the occupations and/or industries within classification coding schemes to exposure estimates. Once the subjects' work histories are coded to the same scheme, the JEMs can be used to obtain exposure estimates for each reported job. The estimates of exposure intensity are increasingly being derived from measurements. Table 1 lists population-based JEMs that incorporated measurements in the development of their exposure estimates. The number and type of agents covered by these JEMs varied. Although some were single-agent JEMs, most included 25 or more agents. The JEMs were developed for a wide range of agents, including silica, asbestos, formaldehyde, chlorinated solvents, metals, gasoline, noise, and ionizing radiation.

The sources of these measurements were varied but included measurements from multiple occupations and industries and spanned decades. Sources have included measurements from regulatory health and safety inspections [3, 4, 5–7], industrial hygienic surveys undertaken

by research, university, medical, and government groups [8–12, 13••,14–16], industry databases and reports [10, 11, 14, 17•], published literature [10, 12, 13••, 18, 19], and unpublished technical reports [12, 13••]. Many of these sources have been compiled into large national and international exposure databases [8, 11, 12, 14, 20, 21]. For example, to develop a noise JEM, Sjöström et al. [14] compiled 145 measurement reports, comprising 569 measurements on 129 occupation groups, from occupational medicine clinics, occupational health services, and large companies in Sweden. The measurements included short duration and full-shift personal and area measurements from 1970 through the 2000s. Several studies noted that data were generally sparse for the earliest time periods [5, 6, 11, 12, 14, 15]. For instance, Peters et al. [11] reported that 1.4% of the data were collected pre-1975 and Vila et al. [12] reported that 33% of the measurement sources described measurements collected in the late 1970s and 1980s and the remainder were from the 1990s and 2000s.

In many JEMs, the measurements were used qualitatively or quantitatively as a starting point for the JEM's exposure intensity metric (e.g., [8, 14–16, 17•, 22]). Usually agent-, occupation-, and time period-specific arithmetic means were calculated and then reviewed by teams of experts. The experts modified the measurement-based estimates for a variety of reasons, including non-representative or sparse data. Additionally, expert judgment was used when measurement data were lacking for an occupation and was often based on data from similar occupations (e.g., [18, 17•, 22]). The coverage of measurements across the exposed occupations and the extent with which the measurements were modified was often not reported. However, if the JEM included a measure of 'confidence' in the metric, the confidence was typically assigned a higher rating for measurement-based estimates and a lower rating for expert estimates [8].

Several JEMs were developed by adapting a pre-existing JEM with region-specific measurements. For example, FINJEM and region-specific measurements were used to develop the New Zealand NZJEM [10], Nordic NOCCA JEMs [15], Spanish MatEmESp [17•], and INTEROCC JEM [22]. In the MatEmESp JEM, the FINJEM estimates were initially assigned as the default exposure values for each occupation in the JEM [17•]. The experts then revised the estimates to best reflect the level of exposure within the Spanish working population, using region-specific exposure data. The New Zealand wood dust JEM based 40% of the estimates on national survey data, 23% on exposure measurements from New Zealand work sites, and 37% from overseas exposure data and available JEMs, such as FINJEM [10].

Intensity estimates within a multi-country JEM developed to assess exposure to power-frequency magnetic fields were derived primarily from measurement data [18]. The database comprised 2,317 measurements from five countries that were obtained from seven sources, including six exposure monitoring studies with access to the original data, plus supplemental data from three published studies extracted as summary measures. The largest source was a monitoring study conducted on a population-based random sample of 1,098 Swedish men [23]. The data were used to calculate arithmetic means, geometric means, and geometric standard deviations that were weighted based on the number of measurements for each occupation group and derived for varying hierarchy levels of the classification scheme (2-,

3-, and 4-digit levels). Estimates for exposed jobs without measurements were inferred from one or more close occupations in the hierarchical classification scheme. Turner et al. [22] enhanced this JEM for the INTEROCC Study by incorporating additional measurements.

To provide a mechanism to assign measurement-based estimates to occupations and time periods that had no or limited measurement data, a statistical model framework was developed to calibrate ordinal expert-based JEM intensity estimates to a concentration scale across time and applied to eight chemical agents [5, 6, 24, 25••]. The framework combined JEM ratings and measurements in a mixed-effects model that treated the JEM rating and calendar year as fixed effects and treated group-level variables (e.g., occupation, industry and/or region) as random effects to account for clustering and correlations within the data. This structure allowed the extraction of time period- and rating-calibrated JEM estimates when the fixed effects were used. Group-specific estimates could also be obtained by using both the fixed-effects terms and the best linear unbiased predictors from the group-specific random effects. The group-specific estimates were a 'shrinkage estimate' that was a weighted average of the group-specific estimate and an estimate based on all measurements with the same rating, with weights varying based on the number of measurements and the measurements' variability.

The above mixed-effects model framework was used to assess exposure to five agents in the SYNERGY case-control study of lung cancer [24, 25••] and for three agents in the Shanghai Women's Health Study, a prospective cohort of Shanghai women [5, 6]. The Shanghai Women's Health Study models used a database of health and safety inspection area air measurements collected over more than four decades, with >60,000 benzene measurements [5] and >10,000 lead fume and >5,000 lead dust measurements [6]. This inspection database provided no ancillary data other than job, industry, sample location, and factory name. The SYNERGY models were developed using the ExpoSYN database, which included 356,551 measurements from 19 countries for five chemical agents that spanned more than five decades, with ancillary data on job characteristics and measurement information [11, 24, 25••]. The ExpoSYN measurements were compiled from national exposure databases (90%), research institutes (8%) and industry-specific databases (1%) [11]. Group-specific estimates derived from the applications of this model framework provided greater contrast between individuals in the final exposure estimates than could be obtained by using only the expert JEM ratings, with greater contrast observed when more measurements were available [5, 6, 25••]. Varying uses of these models to derive group-specific estimates, calibrated JEM estimates, and uncalibrated JEM estimates on a concentration scale resulted in robust exposure-response associations and similar model fits in sensitivity analyses that compared the lung cancer risk from respirable crystalline silica exposure [26] and risk of non-Hodgkin lymphoma from benzene exposure [27••]. As a result, the group-specific and calibrated JEM estimates had the advantage of providing quantitative exposure-response curves that will aid risk analyses.

Most uses of measurement database have focused on estimating exposure intensity; however, some have used measurements or survey data to estimate the probability or prevalence of exposure within each occupation group. To develop a beryllium JEM, Hamm and Burstyn [3] predicted the probability of occupational beryllium exposure exceeding specified

thresholds (e.g., $>0.1 \mu\text{g}/\text{m}^3$, $0.5 \mu\text{g}/\text{m}^3$) using 12,148 personal measurements of beryllium exposure obtained from the US Occupational Safety and Health Administration's (OSHA) inspection measurement database. The focus on probability occurred because a large proportion of the data were below the limit of detection and because of the non-random nature of the OSHA monitoring strategy. Probability of a measurement exceeding the set exposure threshold was predicted using a Poisson regression model that incorporated year, industry, job, and sampling duration as exposure determinants. Similarly, to develop a PAH JEM from coal tar pitch volatile measurements obtained from the same US OSHA database, Lee et al. [4•] used a mixed-effects logistic model to predict the probability of exceeding OSHA's permissible exposure limit for PAHs based on industry and occupation. Compliance inspection number was included in the model as a random effect to account for correlated data.

Job-by-job review and exposure decision rules

The previous JEM-based approaches assume all jobs within the same standardized occupation group have the same exposure; however, many studies have collected more detailed occupational information that can be used to develop task- or subject-specific exposure estimates. The more detailed information predominantly comes from the inclusion of exposure-oriented questionnaires that target the tasks and exposures for jobs and industries of interest. Given the more detailed and complex exposure information available, exposure assessment efforts in these studies have often been conducted using expert review of each job, or exposure decision rules that link questionnaire responses to exposure estimates, or combinations of the two approaches [1]. These estimates of the probability, intensity, and frequency of exposure were usually obtained using expert judgment, with their ordinal or semi-quantitative assessments of exposure intensity supplemented by qualitative and quantitative review of the published literature. For example, over 500 peer-reviewed articles and technical reports were summarized by job and decade to develop occupational lead estimates for participants in a case-control study of meningioma and glioma [28].

To assist with the experts' development of exposure intensity estimates, exposure databases have been extracted and summarized in published literature reviews for several agents, including metalworking fluids [29, 30], diesel exhaust [31], trichloroethylene [32], benzene [33], perchloroethylene [34], hydrocarbon solvent exposure [19], and lead [35]. The source of these measurements have included the published literature, NIOSH Health Hazard Evaluations (detailed reports of one or multiple facilities), and NIOSH Industry-wide Studies reports (reports investigating typical exposure levels within specific industries). For example, a database of occupational lead measurements from U.S. work sites included 1,111 sets of lead summary statistics reported in the published literature representing $>7,900$ personal air measurements, $>5,700$ area air measurements, and $>19,500$ blood measurements from 175 papers published between 1940 and 2010 [35]. The database included ancillary exposure-related information, including job, industry, task/location, year collected, sampling strategy, control measures in place, and sampling and analytical methods.

The reported concentrations in the published literature are usually reported as summary measures (e.g., arithmetic and geometric means) and measures of exposure variability (e.g.,

range, geometric standard deviations). Methods to analyze these data have accounted for the number of measurements [36, 37, 38•] or both the number of measurements and their variability [39, 40, 41••]. The latter approaches include simulation of the individual measurements from the summary measures [39] or the use of mixed-effects meta-regression models to combine summary measures from multiple sources [40, 41••].

Several statistical models have been developed specifically for population-based studies with more detailed exposure information to aid the assignment of exposure intensity estimates on a continuous scale. For example, Hein et al. [36, 37] developed agent-specific models for six solvents to estimate historical exposure using predictors based on industrial hygiene principles. These predictors included operation/activity, primary and secondary mechanism of exposure release into the air, presence of local or general exhaust ventilation, process conditions (e.g., temperature, usage rate, open or closed systems, quantity of material), work location, and distance to source. These models were used to assign exposure intensity estimates in task exposure matrices for solvent-exposed tasks (e.g., degreasing, dry cleaning, lab work, hospital care, plastic manufacture) that were then applied to participants in two studies, a case-control study of brain cancer [42] and a case-control study of kidney cancer [43]. Assignment of the predictors to the subject-reported information to obtain exposure intensity estimates required expert judgment of the likely work conditions, as the questionnaires did not directly ask about these conditions.

Similar models were developed to estimate exposure based on surrogate measures that were more directly extractable from the occupational questionnaires. For example, historical metalworking fluid concentrations for participants in a case-control study of bladder cancer were obtained from a model that included industry, type of metalworking fluid, and type of operation (grinding vs. other) [38•]. The exposure-response relationship for straight metalworking fluids in this case-control study was remarkably similar to the exposure-response relationship obtained in a cohort study of autoworkers [44]. This demonstrated that it was possible to develop quantitative estimates in population-based studies that are comparable to the high quality assessment efforts in industry-based studies.

Measurements were the primary source for the development of an electromagnetic field (EMF) source-specific exposure matrix for 312 EMF sources that could be linked to exposure sources reported by study participants in questionnaires [12, 13••]. The measurement database included 1,624 sets of measurements collected between 1974–2013 for 285 EMF sources obtained from 95 literature reports from 16 countries, of which 35% were unpublished technical reports. Experts rated each measurement record on a scale of 0 to 3 for eight characteristics, including sample size and sampling strategy, to assess the quality and relevance of the measurements. The measurements were combined, weighted by the experts' average confidence, using order statistics and log-normal distribution characteristics to calculate arithmetic mean, geometric mean, and estimates of exposure variability and maximum exposure for each source.

The measurements used to aid exposure reconstruction efforts have been primarily based on air measurements. However, recently, the use of mixed-effects meta-regression models based on published blood lead measurements was reported [40, 41••]. Analyses of these published

concentrations were generally limited to extracting job-, industry-, and time period-specific exposure concentrations despite the availability of additional ancillary data, which were generally too sparse to characterize or collinear with other variables.

National exposure databases, such as the German MEGA exposure database and the French COLCHIC database, have also been used to develop occupation-, industry-, and time-specific exposure profiles that can aid future exposure assessment efforts in population based studies. The MEGA database includes over 1,000,000 measurements of over 400 substances from 1972 onwards, with up to 150 pieces of information, such as type of workplace, working conditions, measured substances, sampling strategy, sampling duration, and sampling and analytical method [21]. Subsets of the MEGA database have been used to develop exposure profiles for inhalable nickel air exposure [45•] and hexavalent chromium [46]. The COLCHIC database was set up in 1987 and includes measurements from French interregional laboratories and the French national and safety institute laboratories; by 2001 it contained over 400,000 measurements for over 600 substances [20]. Subsets of the COLCHIC database have been used to develop exposure profiles for formaldehyde [7, 47] and mineral fibres [48]. It has also been used to develop TEXAS, a Tool for EXposure ASsessment, to obtain rapid estimation of the level of exposure control as a function of simple determinants of work situations for 26 chemical substances [49•].

Discussion

Exposure assessment in population-based studies is increasingly using exposure measurements both qualitatively and quantitatively. These efforts have been facilitated by extensive work in compiling databases of measurements from multiple sources that represent multiple occupations, industries, and long time spans. The direct use of these measurements as exposure intensity estimates improves the transparency of the exposure assessment process and creates mechanisms to update the estimates with additional data (e.g., incorporating region-specific measurements). It also allows for the calculation of measures of exposure variability, rather than solely point estimates. The resulting intensity estimates allow for estimation of quantitative exposure-response relationships. The variability measures could be used in sensitivity analyses and evaluations of measurement error and its impact on the observed associations.

The long time span of measurement coverage needed for population-based studies of cancer and chronic diseases creates several challenges in compiling, analyzing, and using these data sets. Statistical and interpretation challenges can occur because measurement and sampling methods change over time. Similarly, sampling strategies vary across and within study sources and across time. Availability of ancillary data to account for these differences was highly variable. For example, Peters et al. [11] reported that the amount of missing information on the reasons for measurement collection (e.g., survey, inspection/complaints, compliance) varied across the five agents in the ExpoSYN database, ranging from 18% for PAH to 58% for asbestos. Statistical challenges occur when using laboratory sources of measurements, especially for analytes measured as part of a panel; these approaches will need to consider whether the non-detected samples represent ‘present but not quantified’ or ‘absent’ [50•]. Statistical challenges also occurred when combining individual

measurements and exposure concentrations reported as summary measurements [36, 37, 38•, 39, 40, 41••] and when combining expert judgment with measurement data sources [5, 6, 24, 25••]. Adaptation of Bayesian and other methods to combining these varying sources may be needed. For example, when data is limited and multiple experts provide independent exposure estimates, one could extend the Bayesian framework developed by Ramachandran et al. [51–53] for industry-based exposure assessment. This approach used the expert ratings as exposure priors and used measurement data to update the posterior exposure distributions.

The availability of measurement data will vary by geographic region, and development of a region-specific database is not always feasible. However, the generalizability of region-specific measurement data should be addressed prior to application to other regions. In several studies, measurements from a different geographic area were supplemented with region-specific data, when available, and modifications were sometimes made for region-specific factors such as time trends and occupational groups [10, 15, 17•, 22]. This is a practical approach for addressing data limitations.

There have been limited evaluations of potential systematic biases and representativeness of these measurement sources. A comparison of the French COLCHIC database containing inspection measurements with the SCOLA database containing measurements focused on prevention found that the median concentrations were over three times higher in COLCHIC than in SCOLA; however, the differences were attenuated once sampling duration was taken into account [54]. In contrast, comparisons of the COLCHIC and US OSHA IMIS inspection databases provided similar multi-industry portraits of formaldehyde exposure despite a potential for very different occupational settings [7]. A review of evaluations of US OSHA measurements found that no biases were consistently reported across studies or agents [50••]. However, comparisons of two sources of US OSHA measurements, an inspection database and a laboratory database, found only 39% of the lead measurements were reported in both databases [50••]. The percentage of samples below the limit of detection was much higher in the measurements only occurring only in the laboratory database (71% non-detects) versus only in the inspection database (46%) or in both databases (42%). The authors concluded that these differences likely represented differential under-reporting of non-detects in the inspection database as well as the inclusion of measurements in the laboratory database that were analyzed as part of a panel sample when the agent of interest may have been another agent on the panel. Subsequent evaluations of measurements in the inspection database for 77 agents found that exposure concentrations varied by purpose of inspection, type of OSHA plan (state vs. federal), and past history of penalties [55]. Concerns regarding data quality and large proportions of samples less than the limit of detection led some researchers to model the probability of exceedances over exposure thresholds, rather than quantitative exposure concentrations [3, 4•]. Overall, these comparisons between sources have been hampered by the lack of gold standards that represent population-level average exposure patterns. Measurements and survey responses from random samples of the working population would assist these evaluations; however, those findings may not extend to the historical time periods of interest in most of these studies.

Conclusions

In population-based studies, quantitative measurement-based exposure assessment approaches are increasingly replacing expert judgment of exposure intensity and, in some cases, exposure probability. These efforts facilitate quantification of exposure-response associations. Future efforts should consider incorporating the measures of exposure variability into uncertainty analyses. Evaluations of potential biases in these measurement sources, and their representativeness of typical exposure situations, warrant additional examination.

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•• Of major importance

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Table 1

Published population-based job-exposure matrices (JEMs) that have reported use of measurement data

Reference [Citation no.], JEM name if applicable	Geographic region	Agent(s)	No. and source of measurements	How measurements were used
Bowman et al. 2007 [18]	Finland, Italy, New Zealand, Sweden, United States	Power-frequency magnetic fields	2,317 measurements compiled from original monitoring data and summary statistics from 10 published studies	Calculation of job-specific summary statistics of workday-average exposures
Fevotte et al. 2011 [16], Matg��n�� JEMs	France	5 organic or mineral dusts, 3 mineral fibers, 7 petroleum-based solvents, 5 chlorinated solvents, 4 oxygenated solvents, formaldehyde, PAH	French exposure databases; international literature	Considered by experts as part of the expert judgment process ^d
Friesen et al. 2012 [5]	China	Benzene	63,037 measurements from regulatory health and safety inspections	Statistical modeling to derive calibrated JEM ratings and group-specific estimates
Garcia et al. 2013 [17��], MatEmESp JEM	Spain	39 chemical agents, 2 physical agents	industrial hygiene surveys and measurements from Spanish companies	Refinement of FINJEM estimates with region-specific data
Hamm and Burstyn 2011 [3]	United States	Beryllium	12,148 measurements from regulatory health and safety inspections	Statistical modeling to predict probability of exceeding a set exposure level
Kauppinen et al. 1998, 2014 [8–9], FINJEM	Finland	12 physical agents, 48 chemical agents, 2 microbiological agents, 8 physiological/ergonomic factors, 9 psychosocial factors, 5 lifestyle factors	157,035 chemical exposure measurements from Finnish exposure databases and surveys	Considered by experts as part of the expert judgment process
Kauppinen et al. 2009 [15], DANJEM, ICEJEM, NORJEM, SWEJEM	Denmark, Iceland, Norway, Sweden	24 chemical agents, 4 non-chemical factors	national exposure databases	Refinement of FINJEM estimates with region-specific data
Koh et al. 2014 [6]	China	Lead dust, Lead fume	5,383 lead dust and 20,084 lead fume measurements from regulatory health and safety inspections	Statistical modeling to derive calibrated JEM ratings and group-specific estimates
Lee et al. 2015 [4]	United States	PAH	2,509 measurements from regulatory health and safety inspections	Statistical modeling to predict probability of exceeding a set exposure level
Peters et al. 2011, 2012, 2016 [11, 24, 25��], SYN-JEM	Bulgaria, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Italy, The Netherlands	Asbestos, Chromium-VI, Nickel, PAH, RCS	ExpoSYN: 356,551 measurements from national and industry-specific databases and institutional data	Statistical modeling to derive calibrated JEM ratings and group-specific estimates
Sjostrom et al. 2013 [14]	Sweden	Noise	569 measurements from Swedish occupational medical clinics, occupational health services, and large companies	Considered by experts as part of the expert judgment process
t' Mannelje et al. 2011 [10], NZJEM	New Zealand	Wood dust	200–300 wood dust measurements from New Zealand workplaces. Additional	Considered by experts as part of the expert judgment process

Reference [Citation no.], JEM name if applicable	Geographic region	Agent(s)	No. and source of measurements	How measurements were used
			measurements from overseas exposure data and JEMs	
Turner et al. 2014 [22] (<i>enhancement of JEM used in Bowman et al. 2007</i>)	Australia, Canada, France, Germany, Israel, New Zealand, United Kingdom	Extremely low-frequency magnetic fields	summary statistics and primary data from published studies	Calculation of job- specific summary statistics of the workday-average exposures
Vila et al. 2016a,b [12, 13••], Source-Exposure Matrix (SEM)	16 countries	312 sources of Electromagnetic fields (EMF) exposure	3,141 measurements from published literature and unpublished technical reports	Calculation of confidence-weighted mean exposure statistics for each EMF source

No., number; PAH, polycyclic aromatic hydrocarbons; RCS, respirable crystalline silica

^aInformation regarding how the measurements were used by the experts was not fully described, but may include qualitative evaluation of multiple data sources, direct use of the mean concentration when data was sufficient, or expert-based modifications to the measurement data (such as analogy through similar jobs or modifications to account for time-period effects).