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Retrospective exposure assessment in a chemical research and development facility

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ABSTRACT

The objective of this exposure assessment was to reconstruct cumulative historical exposures for workers who have been exposed to multiple chemicals and chemical groups to better understand a cluster of brain cancers within a research and development lab. Chemicals of interest, including acrylates, bis-chloromethyl ether (BCME), chloromethyl methyl ether (CMME), isothiazolones and nitrosoamines, were selected on the basis of the plausibility of penetrating the blood–brain barrier and the uniqueness of the chemical's biological activity.

In a complicated exposure setting such as a chemical R&D facility, multiple exposure estimation methods were needed. First, similarly exposure groups (SEGs) were created for these materials based on department group, time period of the department's existence and function associated with job titles. A probabilistic framework for assessing exposures was developed using Bayesian analysis of historical monitoring data, mathematical exposure modeling and professional judgments of current and former industrial hygienists at the facility were used to reconstruct the exposure history for acrylates, BCME and CMME for each SEG over the time period of interest. Since sufficient measurement data for isothiazolones and nitrosoamines were not available, the exposure histories for each SEG for these chemicals were estimated. This was done using objective formaldehyde levels and subjective employee interviews. The interviews assessed workplace determinants of exposure as distinct surrogates for estimating inhalation and dermal exposures. The exposure assessments by these methods were compared against each other to estimate the potential for exposure misclassification. A job exposure matrix (JEM) was constructed that contained the exposures obtained from above multiple approaches for each of these chemical groups for each SEG for each year of interest. The combination of methods used in this work is a unique and potentially helpful framework that can be used in analogous workplace settings involving multiple exposures with incomplete objective measurement information.

1. Introduction

In 2001, Rohm and Haas (R&H) Company became concerned about the presence of brain cancer at the Spring House research and development facility. This concern was triggered by several brain cancer cases in young chemists at Spring House that were diagnosed, along with reports of brain cancers at another petrochemical research facility reported in the same time period (Beall et al., 2001; Delzell et al., 1999; Rodu et al., 2001; Sathiakumar et al., 2001). This paper reports on the exposure reconstruction that was undertaken as part of an epidemiological study of the relationship between excess brain cancer and occupational chemical exposures for employees at the R&H facility.

The objective of the epidemiological study was to evaluate overall mortality, and specifically brain cancer mortality in employees of the facility. A mortality study was conducted on 5284 workers who had ever been administratively assigned to the facility. A nested case–control study was conducted to evaluate brain cancer risk associated with specific jobs and chemical exposures. The mortality study identified 486 deaths including 14 brain cancer deaths. Four controls were selected for each case using an incidence density sampling protocol. Exposure was estimated up to the date of death for the case for both cases and matched controls. The analysis included the entire exposure history and also lagged the exposure by 10 years. The results of the epidemiology study will be reported elsewhere.

Reconstructing historical exposures to chemicals is challenging due to the limited quantity of exposure monitoring data available. In such instances, the available measurement data need to be supplemented with exposure estimates based on exposure modeling and expert judgments that are based on workplace information. Monitoring data or mathematical modeling can be used either informally or in a formal Bayesian framework to reconstruct the exposure history (exposure as a function of time) and estimate cumulative exposures (Felten et al., 2010; Friesen et al., 2006; Glass et al., 2000; Ramachandran 2001; Ramachandran and Vincent 1999; Stewart et al., 2003). Some studies have used exposure modifiers to estimate historical exposures by making adjustments to current data based

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on changes in exposure determinants, e.g., changes in the process, ventilation, and use of personal protective equipment (Esmen 1979; Lagorio et al., 1993; Schneider et al., 1991). The estimates obtained from any of these methods can be arranged in a job exposure matrix (JEM) for use in epidemiological analysis (Dick et al., 2010; Hopf et al., 2009; London 1998; Young et al., 2004).

In addition to the lack of objective monitoring data, there are several aspects of this study that presented unique and interesting challenges. The overall epidemiologic evidence for brain cancer risk related to chemical exposures is not consistent, and its specific causal agents remain, for the most part, unknown (Beall et al., 2001; Bondy and Lee Ligon 1996; Cooper et al., 1997; Haidar et al., 2008; Longstreth et al., 1993; Marsh et al., 1999; Mazumdar et al., 2008; Samanic et al., 2008; Samkange-Zeeb et al., 2010). The problem of identifying a potentially-causative agent is further compounded by the large variety of chemicals typically used at this R&D facility over time.

The exposure assessment presented in this paper has several novel features: a systematic framework for identifying chemicals of relevance to brain cancer, a methodology for creating SEGs in a non-traditional occupational setting, multiple approaches to assessing exposures including Bayesian analysis of available monitoring data, mathematical exposure modeling, eliciting professional judgments, and developing exposure modifiers based on relevant exposure determinants. We compare these methods against each other to assess potential for exposure misclassification.

2. Materials and methods

The first two tasks were to classify the workers into similarly exposed groups and then to select the chemicals on which to focus attention. Five chemical groups were selected, as described below. For three of these groups, a Bayesian approach was used for exposure reconstruction that incorporated information from monitoring data, exposure models and expert judgment. For the other two chemical groups, sufficient information was not available to use this approach. Therefore, we developed two exposure surrogates that provided relative exposure levels. The following sections describe these methods in greater detail.

2.1. Description of research facility

The R&H facility was established in 1963, to house research and development laboratories. The facility developed specialty chemicals with specific expertise in chemicals for leather tanning, organic pesticides, biocides, ion exchange resins, emulsions, plastic additives, coatings, adhesives, sealants, and pharmaceuticals. Thousands of chemicals in the above categories have been used, synthesized, formulated and applied in the research facility for different purposes. The research labs and offices occupy 11 buildings totaling over 20 acres. The facility has employed over 5200 scientists and support staff who were assigned to the Spring House Research facility since 1963.

2.2. Construction of SEGs

Employment records identifying job title, department, and dates of employment were obtained to classify workers into similarly exposed groups (SEG). A relatively small number of job titles were present across the facility but their functions and tasks differed by department. To create SEGs, we first mapped the jobs to "functions" within each department. The three primary functions included synthesis of new chemicals (synthesis), or combining chemicals to create new products (formulation), and handling chemicals and custom tailoring them for customers (tech services). There were seven additional functions that included administrative, analytical services, applications (formulations and tech services), synthesis and/or applications, synthesis and/or formulations, maintenance, and toxicology service functions. Another unique feature of this facility is that it has a large number of departments that were created to meet specific needs relating to new products or new areas of research. The number of departments was reduced from 187 to 25 by grouping similar departments into "department groups". Both of these changes were made with inputs from Spring House industrial hygienists (IHs) who also consulted with current and former employees with detailed knowledge of the various departments.

Fig. 1 schematically shows the approach for constructing SEGs. Seventy-seven distinct SEGs were identified by mapping the department groups to the given functions (for job titles) within various time periods from the 1960s to the 2000s. Table 1 shows department groups, departments, time periods of departments, and functions across Spring House.

2.3. Identifying chemicals for analysis

Spring House employees worked with literally tens of thousands of chemicals, thus it was necessary to narrow the list of chemicals on which to focus. Several criteria were used for this purpose: (1) physical and chemical properties of the chemicals, especially the fat solubility (log (K_{ow}) > 2) and volatility (vapor pressure) of the chemical (VP > 1 mm Hg), allowing us to focus attention on substances that had a reasonable chance of crossing the blood–brain barrier; (2) mention in the peer-reviewed literature that a given chemical that was used at the facility and may have links to central nervous system (CNS) effects, especially brain cancer, based on human (Beall et al., 2001; Rodu et al., 2001; Sathiakumar et al., 2001; Thomas and Waxweiler 1986) and animal studies (Garrison et al., 2002); (3) chemicals that were unique to the facility and had not been extensively studied in other settings; (4) inputs from company technical staff and stakeholder groups. Many common solvents that may have CNS effects were excluded since these have been studied in other industry sectors where their use was more prevalent. The criteria mentioned above were used in a step-wise manner, where each criterion was used as a filter to short list some chemicals that would then be subjected to the next criterion. On the basis of the first two criteria, we narrowed the list from several thousand chemicals to 74 chemicals in 20 groups. Using criteria (3) and (4), we were able to narrow the list further to the following five chemical groups: acrylates, bis-chloromethyl ether (BCME), chloromethyl methyl ether (CMME), isothiazolones, and nitrosoamines.

2.4. Sources of exposure data

The information on exposure data was obtained from several sources:

(1) Exposure monitoring data
Personal exposure and area monitoring data have been obtained at the facility by IHs since the 1960s and were recorded in a company database called the Employee Exposure Monitoring System (EEMS) that contains more than 7500 monitoring records. All of sampling was carried out by qualified industrial hygienists and analysis carried out by accredited laboratories following standard methods. While some SEGs had a large number of monitoring data over the years, many SEGs had very few. Among the chemicals selected, acrylates had the most available data, followed by BCME and CMME. However, isothiazolones and nitrosoamines had very few data. Nitrosoamines were monitored only once since the 1960s. While it would have been useful to understand the sources of exposure variability and apportion it as between- and within-worker variability, this was not feasible with the EEMS database. Individual workers were not identified in the