EXPOSURE RECONSTRUCTION FOR A BRAIN CANCER EPIDEMIOLOGICAL STUDY IN SEVEN CONNECTICUT JET ENGINE MANUFACTURING FACILITIES

Executive Summary

1. Project Overview and Specific Aims

The purpose of this exposure reconstruction study is to develop assessments of historical processes and exposures in seven Pratt and Whitney facilities involved in various aspects of jet engine development, manufacture, and repair. This information will be used in the concurrent cohort epidemiology study conducted by the University of Pittsburgh to identify possible causes of a possible excess incidence of glioblastoma multiforme. The proposed study will reconstruct potential worker exposures for a wide variety of process-related substances (solvents, metals, oils, etc.), tasks and operations. As in any estimation process, the model estimates will have to be verified by existing exposure data where available or appropriate and/or by actual physical modeling of the task when data are not available. From these verified models, exposure estimates for each distinct task will be developed. Task exposure estimates will then be assigned to occupations based on the tasks performed and the time spent performing each task.

The final product of this project will be a "job/exposure dictionary", in which each job title in each time period will be assigned an estimated exposure to each identified toxicant. These estimates will be used by the University of Pittsburgh group in its epidemiologic analysis to develop a cumulative exposure estimate for each individual that will reflect their historical exposure.

The specific aims of this study are to:

- Identify and describe the production processes used at the seven different production facilities;
- Identify all materials used in the production processes;
- Define each specific task associated with the production processes for each end product;
- Identify occupations and their associated tasks;
- Collect all available exposure data and enter it into database;
- Define the expected range of exposures for each task and time period using both mathematical and physical modeling;
- Verify model estimates with exposure and physical modeling data;
- Develop task and time-specific estimates of exposure for each toxicant;
- Develop cumulative exposure estimates for job title during each time period.

2. Study Resources

The study will be conducted by Dr. Nurtan Esmen and his coworkers in the Department of Occupational and Environmental Health of the College of Public Health at the University of Oklahoma Health Sciences Center.

3. Research Plan

Though the epidemiologic literature suggests an association between brain cancer and a variety of occupations and/or imputed occupational exposures, with the exception of ionizing radiation and possibly certain N-nitroso compounds, the evidence for any particular causative agent ranges from weak to nonexistent. Because no single agent or combination of agents is strongly suspect based on previous studies, in this study all agents present in the workplace must at the outset be treated as potentially causative. An attempt to obtain a refined exposure reconstruction for the entire set of agents would, however, be totally unrealistic in terms of the time and costs involved. Because we do not have a guideline for a priori selection of a group of agents and/or processes, we must instead adopt a more exploratory approach to the problem. The range of potential suspect agents and/or processes will be progressively narrowed down in a stepwise fashion that will require coordination between the exposure reconstruction study at the University of Oklahoma and the epidemiology study at the University of Pittsburgh. To eliminate any chance of bias in this process, each group will remain unfamiliar with the data structure of the other group. In other words, the researchers doing the epidemiologic are not allowed to change the exposure results, and similarly, the exposure construction effort is totally blind to the occurrence or absence of brain cancer in any individual member of the cohort.

The first step in the exposure reconstruction will be the collection of information on the processes, jobs and tasks at each of the seven facilities included in this study: Cheshire, East Hartford, Manchester Foundry, Middletown, North Haven, Rocky Hill, and Southington. This information will be gathered from documents preserved in the company records, such as operation manuals, specification sheets, engine build sheets, environmental reports, etc., and from interviews of engineering and production personnel. Exposure monitoring records will also be collected, and long-time employees will be interviewed about historical work practices and processes; this information will be used in the latter part of the study to develop quantitative estimates of exposure.

Using the process information collected, we will create a preliminary job dictionary in which exposures to specific agents and/or processes will be assigned to job classes strictly as an "exposed/not exposed" dichotomy. Many of the exposures, especially those related to metal aerosols, oil fumes and coupled generation of more than one agent, must be defined not only in relation to specific chemical entities but also in relation to the processes generating the agents. Obviously, this approach will result in hundreds of contaminants or contaminant/process combinations to be considered. This would be too chaotic to make sense, and the random

variability in the data would not permit the requisite accuracy to differentiate the influences of the various agents. It will therefore be necessary to screen these hundreds of potential exposures and to select for initial analysis only the agents or combinations that are plausibly suspect. This screening will be based on considerations such as evidence of potential carcinogenicity from existing epidemiologic and toxicological studies, or physical and physiological transport properties of the agents that would enable the agent or its metabolites to reach or influence the cancer site.

The preliminary job dictionary with dichotomous exposure assignments will be completed near the end of the fourth year of the project. The preliminary job dictionary can then be used in conjunction with the preliminary epidemiologic analysis to be performed by Dr. Marsh's group at the University of Pittsburgh. Based on the preliminary analysis, the number of agents and processes will be consolidated for further scrutiny and use in a more defined case control study during the last year of the study.

In the last two years of the project, quantitative estimates of exposure to the selected agents will be developed. The primary exposure metric will be the job- and era-specific time weighted average exposure. We shall not attempt to estimate peak exposure levels because chronic diseases are generally poorly predicted by peak exposures and the refinement necessary for coherent prediction of peak exposures for all agents will be prohibitively expensive both in time and effort. We will use, to the extent possible, all of the exposure data (personal air samples) to quantify exposure during those periods where the exposure data are relevant. The enhancement, interpolation and extrapolation of the extant exposure data will be based on modeling. The modeling will be based on accepted principles of chemistry, physics, engineering, fluid transport, statistics, and physiology. The mathematical models developed will be validated, to the extent possible and necessary, by well-designed experiments using existing industrial operations or laboratory demonstrations, and by comparison to relevant exposure data if available.

It may be noted that an alternative approach based on quantification of expert judgment has sometimes been used in retrospective exposure assessment studies. This approach, which amounts to making an educated guess of the historical exposure levels, will be avoided in this study because such methods lack logical and theoretical rigor and have been found to be unreliable. If expert judgment is used at all in this project, it would figure only within a limited context and only as a last resort in specific cases if a limited amount of historical exposure data were available but objective mathematical and physical modeling were not feasible.

The final product of this project will be the refined job/exposure dictionary, which will be delivered to the University of Pittsburgh group around the midpoint of the final year. After this point the University of Oklahoma group will continue to confer with the University of Pittsburgh group as needed to resolve any inconsistencies in such matters as the definitions of job titles and historical eras; however, to ensure the scientific integrity of the study, at no time would the exposure estimates be altered based on the epidemiologic outcomes.