Epidemiology and Biostatistical Component of the Pratt & Whitney Exploratory Cohort Mortality Study

Executive Summary

1. Background

In May 2000, the Connecticut Department of Public Health (CDH) began an investigation of a suspected cluster of brain cancer at the Pratt & Whitney (P&W) jet engine manufacturing plant in North Haven, CT. A preliminary comparative cancer incidence analysis conducted by the CDH was inconclusive, and CDH recommended that a more comprehensive and rigorous investigation be undertaken by an independent research group. In August 2001, at the recommendation of the Connecticut Department of Health and the National Institute for Occupational Safety and Health (NIOSH), Drs. Gary M. Marsh of the University of Pittsburgh, Department of Biostatistics (UPitt) and Nurtan A. Esmen of the University of Oklahoma, Department of Occupational and Environmental Health (UOk) were asked by P&W to evaluate the feasibility of conducting a formal epidemiologic investigation of the suspected brain cancer excess.

The feasibility study found that sufficient demographic and work history data are available to conduct an historical cohort mortality study and a brain cancer incidence study of former and current workers from North Haven as well as six other P&W manufacturing sites that operated or currently operate in the south-central CT area (in alphabetical order): Cheshire, East Hartford, Manchester Foundry, Middletown, Rocky Hill, and Southington. Other plant sites were chosen: to mitigate certain methodological issues associated with assigning appropriate influence to the original North Haven "index" cases of brain cancer that precipitated the investigation; to afford better opportunities for contrasting cohort attributes, work practices and exposures; to capitalize on the geographically-related homogeneity of the cohort; and to increase the likelihood of producing informative conclusions about the reality and reasons for the suspected brain cancer cluster.

2. Project Overview

The epidemiology and biostatistical components of the study will be conducted by UPitt (Dr. Marsh, Principal Investigator). The UPitt investigation will include historical cohort mortality and cancer incidence studies and a nested case-control study of malignant and benign brain cancer. The cohort study will be used as the basis for systematically enumerating a well-defined study population of former and current workers and ascertaining from this population all living and deceased cases of primary brain cancer from each study plant. The cohort study will address rigorously the basic question of whether the number of observed brain cancers overall and in each study plant is greater than would have been expected had the death or cancer incidence rates of the general population prevailed on the P&W study population at risk. The cohort study will also enable a comparative mortality analysis of cause of death categories other than brain cancer and will provide P&W a scientific basis for ongoing mortality and cancer incidence surveillance.

The cohort study will also include a nested case-control study of malignant and benign brain cancer. Because the case-control study includes only the known cases of brain cancer and a relatively small set of matched controls (living or deceased study members without a diagnosis of brain cancer), it enables the collection of data on potential risk factors for brain cancer and co-exposures that are unavailable from existing P&W record sources. Thus, compared to the cohort study, the case-control study affords a more comprehensive and focused evaluation of brain

cancer occurrence in relation to demographic, work history and occupational exposures while controlling for potential confounding factors. The case-control analysis will be used to compare cases and controls with respect to the frequency of the various occupational factors of interest. Occupational factors occurring more frequently among cases than controls (after adjustment for potential confounding factors) are potential occupational risk factors for brain cancer.

The UPitt investigation will be complemented by a companion exposure assessment project, which will be conducted independently by investigators at the UOk (Dr. Esmen, Principal Investigator). This comprehensive exposure assessment will attempt to characterize the historical work practices and exposures that occurred in each P&W study plant. UPitt will use this work history and exposure information to examine the relationship between brain cancer mortality and incidence and the past working environment of the P&W study plants.

3. Specific Aims

The primary research objectives of the proposed UPitt investigation in approximate order of execution are:

- To enumerate systematically a complete study cohort of persons who were ever employed at the North Haven plant from its start-up in 1952 until the end of 2001 and to extend this study cohort and minimum cohort entry date to include workers from six other P&W facilities that operated in the central CT area.
- To identify and confirm systematically any additional malignant, primary brain cancer cases and deaths that may have occurred among subgroups of the P&W workforce not covered by the CDH preliminary investigation.
- To determine whether the total number of observed malignant and/or benign brain cancer cases and/or deaths is greater than the number expected based on standardized comparisons with the general populations of the total U.S., the state of CT and the local counties from which the workforces are drawn, and to determine whether any observed excesses are likely to be due to chance factors alone (i.e., are they statistically significant).
- To examine via the historical cohort study and a nested case-control study of brain cancer the relationship between demographic, work history and occupational exposures and the occurrence of malignant and benign primary brain cancer, with adjustment for potentially confounding factors.
- To investigate the total and cause-specific (other than primary brain cancer) mortality experience of current and former P&W workers from each of the study plants as compared to the experience of the total U.S., the state of CT, and the local counties from which the workforces are drawn, with adjustment for potential confounding factors.
- To provide a basis for ongoing mortality and cancer incidence surveillance of the P&W CT workforce.

Considering how little is known about the etiology of brain cancer, it is not surprising that no specific occupational factors at the North Haven or other P&W study plants (i.e., exposures to specific agents or particular job assignments) have been implicated as risk factors for the perceived brain cancer excess. Thus, the case-control study (as well as the historical cohort study) will be *exploratory* in nature and will not attempt to test any specific etiologic hypotheses. As an exploratory investigation, the case-control study will examine a number of general occupational factors associated with working at one or more of the study plants (e.g., year of hire, work area, job title, duration of employment, and the time since first employment). It will also examine specific occupation exposures using data from the companion UOk exposure assessment project. To avoid spurious associations between brain cancer and these occupational factors, careful consideration will be given in the case-control study to the identification and analytic control of known or suspected risk factors for brain cancer.

While the UPitt cohort and case-control studies may provide useful clues about the reason for the perceived brain cancer excess at the North Haven plant, there is no guarantee that useful clues will be identified. In fact, no *single* epidemiological study, despite its size or scope, can guarantee that one or more etiologic agents for brain cancer will be identified.

4. Research Plan

This investigation will be conducted over a a six-year period beginning July 2002 and ending June 2008. During this period, the UPitt and UOk principal investigators will submit semi-annual reports to P&W describing the operational progress of the study.

During project years 01-04, UPitt will collect and process study data in the following plant order: North Haven, Cheshire, Rocky Hill, Manchester Foundry, East Hartford, Southington and Middletown. Because they were involved in different manufacturing processes, the Rocky Hill and Manchester Foundry plants will provide a good contrast of cohort attributes, work practices and exposures compared with the North Haven plant. Each of the remaining plants will provide a comparison to North Haven as they were involved in many similar operations and manufacturing processes.

In project year 05, UPitt will begin descriptive statistical analyses of the cohort and case-control study data. In project year 06, UPitt will begin to integrate into the cohort data base the historical exposure estimates for each plant that will be developed in the companion exposure assessment project conducted by the UOk. Exposure-related statistical analyses of the cohort and nested case-control data will be conducted in project year 06.

At the end of project year 06, UPitt will release and submit for publication our final results for all study plants. If warranted by evidence of sufficient homogeneity, study data will be pooled and analyzed across multiple plants. The second half of project year 06 will also involve additional analyses and the preparation of additional manuscripts, the nature and extent of which will depend on the outcome of the primary analyses.