The Pratt & Whitney Epidemiology Study

Presentation of Final Results

East Hartford, Connecticut
May 23, 2013
Research Teams

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3-Part Presentation

- Part 1: Background / methods of study
- Part 2: Methods / results of exposure assessment
- Part 3: Results / conclusions of study
Part 1a
Background of Study
Background

May 2000 - August 2001

- CT Dept. of Public Health (CTDPH) investigated perceived increase of brain cancer at North Haven (NH) facility

  Identified several cases of primary malignant brain cancer (most were common type, glioblastoma (GB))

  Results deemed inconclusive

  CTDPH recommended comprehensive, rigorous study by independent research group
Background II

August 2001- February 2002
- U. Pittsburgh and U. Illinois at Chicago evaluated feasibility of conducting formal study
- Concluded sufficient data available to study NH and 7 other CT P&W sites

July 2002
- Work began on large, multi-part, exploratory epidemiological investigation
Primary Study Objectives

To determine definitively whether mortality or incidence rates from central nervous system (CNS) neoplasms, including GB, were elevated at NH or 7 other sites:

- E. Hartford, Middletown, Rocky Hill, Southington-Aircraft Rd., Southington-Newell St., Cheshire, Manchester Foundry

To determine definitively whether these rates are associated with specific workplace exposures or experiences
Part 1b
Methods of Study
3-Phase Study

Historical cohort study of workers employed between 1952-2001 at NH or 7 other sites

- **Phase 1**: Mortality study, 222,123 workers, 1952-2004, 68,701 total deaths, 462 CNS cancer deaths (2008)

- **Phase 2**: CNS cancer incidence study, 210,784 workers, 1976-2004, 723 total cases, 277 GBs from 21 state cancer registries (2010)

- **Phase 3**: Are CNS cancer and other causes of death associated with P&W work experiences or exposures? (new results to be published May 23, 2013)
Phase 3 Study Components

- Updated CNS cancer incidence in relation to exposures and work experiences

- Nested case-control study
  - 723 CNS cancer cases age-time-gender matched to 723 controls (non-cases) from cohort
  - Collect data on lifestyle, behavior, medical and occupational history via interview with worker or surviving family member
  - Despite extensive promotion, low participation rates for cases (40%) and controls (18%) precluded analysis of data
  - Provided foundation for more refined exposure assessment not possible at total cohort level
How does updated Phase 3 data compare to Phases 1-2 data?

- Slightly different numbers of observed CNS cancer cases (and deaths) due to changes in cohort member eligibility and additional cases from other state registries.
- Possible to identify work in 5 plant groups: NH, E. Hartford, Southington, Middletown, “All Other”.
- Discontinued use of study factor “payroll type” due to availability of detailed work history and exposure information.
Other Phase 3 Study Components

- Exposure assessment (UIC)
- Updated mortality analysis (non-CNS cancer) in relation to exposures (UPitt)
Data Analysis Strategy

Combined Data

Study factors and exposures/work practices

Subgroups by study factors and exposures/work practices

All workers at risk
1952 (76) - 2001

Work-related factors

Plant group, year of hire, age at hire, duration of work, time since first work, exposures/work practices

Non work-related factors

Race, sex, age group, time period

North Haven workers by study factors and exposures/work practices
P&W Study Highlights

- Remains one of the largest and most comprehensive occupational cohort studies ever done
  - 222,123 workers, 7.6 million person-years of observation

- First large-scale study of jet engine manufacturing workers

- Participation by several groups
  - Scientific Advisory Committee, CTDPH, P&W Union Representatives, Communications Facilitation Workgroup (CFW)

- Results reported in 10 peer-reviewed journal articles
Part 2

Exposure Reconstruction for the Epidemiological Study

May 2013
Exposure Reconstruction

- Defines common exposure subgroups
- Assigns exposures for subgroups
- If there is an excess adverse health effect, then exposure reconstruction seeks an association between exposure and health effect
- If there is no excess health effect, exposure reconstruction, however refined, will not associate an agent with an effect or explain an observation
Exposure Reconstruction Protocol

The study examined:

- All employment categories as defined by the job dictionary
- 11 classes of chemical and physical agents
- 20 part categories
- 16 process categories
Exposure Subgroups: Job Dictionary

• Data came from P&W work history records
  – UPitt provided anonymized combinations of job title, job code, department title, department code, and occupational group from several million lines of data
  – Because many tasks were performed across plants, plant was not considered a critical field for combinations at the cohort level

• 312,646 unique combinations categorized into 42 classes
Exposure Subgroups: Job Dictionary

- No data class: no data in any of the critical fields; not included in analysis
- Null class: less than 1 year total employment and no job title present in record; assigned exposures of “0”
- CANEL: All CANEL-related jobs included for workers with P&W employment after 1966

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of job classes</th>
<th>Working years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>1</td>
<td>28.0</td>
</tr>
<tr>
<td>Intermittent</td>
<td>7</td>
<td>40.7</td>
</tr>
<tr>
<td>Exposed</td>
<td>31</td>
<td>30.5</td>
</tr>
<tr>
<td>CANEL</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Null</td>
<td>1</td>
<td>0.75</td>
</tr>
<tr>
<td>No data</td>
<td>1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

UIC 2013
### TABLE 1. Job Dictionary Classes With Descriptions and Job Title Examples and the Number of People and Working-Years Within Each Cohort-Level Job Class*

<table>
<thead>
<tr>
<th>Job Class</th>
<th>Description</th>
<th>Job Title Example</th>
<th>Number of Workers</th>
<th>Working-Years (All Workers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Intermittent exposed A; research and development</td>
<td>Materials engineer, chemist</td>
<td>15,607</td>
<td>87,317</td>
</tr>
<tr>
<td>IB</td>
<td>Intermittent exposed B; manufacturing supervisors</td>
<td>Foreman, group supervisor</td>
<td>6,867</td>
<td>76,966</td>
</tr>
<tr>
<td>IC</td>
<td>Intermittent exposed C; managers</td>
<td>Industrial hygienist, maintenance engineer</td>
<td>17,498</td>
<td>93,006</td>
</tr>
<tr>
<td>ID</td>
<td>Intermittent exposed D; support and trades</td>
<td>Crib attendant, pipefitter, machine tool mechanic</td>
<td>46,936</td>
<td>295,160</td>
</tr>
<tr>
<td>IE</td>
<td>Intermittent exposed E; engine mechanics and assembly</td>
<td>Engine mechanic, engine assembler</td>
<td>13,410</td>
<td>71,153</td>
</tr>
<tr>
<td>IF</td>
<td>Intermittent exposed F; assembly (other than engine)</td>
<td>Subassembler</td>
<td>11,858</td>
<td>48,703</td>
</tr>
<tr>
<td>IG</td>
<td>Intermittent exposed G; part preparation</td>
<td>Cleaner masker, marker</td>
<td>2,165</td>
<td>8,207</td>
</tr>
<tr>
<td><strong>Total I</strong></td>
<td><strong>Total I</strong></td>
<td><strong>Total I</strong></td>
<td><strong>114,341</strong></td>
<td><strong>680,513</strong></td>
</tr>
</tbody>
</table>
Individually Examined Agents

• Selected based upon:
  – Status as a known or suspected carcinogen (through inhalation, at any organ)
  – Availability of information on usage (how and how much)
  – Availability of industrial hygiene exposure measurements
Individually Examined Agents

Cohort & case-control
1) Chromium
2) Cobalt
3) Solvents
4) Ionizing radiation*
5) Lead-cadmium*
6) Electromagnetic fields*
7) Mineral oil metalworking fluids
8) Soluble metalworking fluids
9) Nickel

Case-control only
1) Polychlorinated biphenyls (PCBs)*
2) Metalworking combustion products specific to North Haven (“blue haze”)

*Qualitative (Yes/No) exposure estimates
Individually Examined Agents

- Generated and validated mathematical models for quantitatively evaluated agents

- Data used:
  - IH sampling measurements
  - P&W engineering time studies

\[
\begin{align*}
\text{COBALT} \\
\text{Background-level job classes:} \\
\text{Exposed job classes: Characteristic exposure groups (CEGs) Characteristic exposure levels (CELS)} \\
\text{CEG}_1 = \text{GAF, GB, GV, GBV, GAF} \quad \text{CEG}_1 = X \in X_1 \quad \text{CEG}_1 = 1.0 \quad \text{CEG}_1 = 0 \quad \text{Else} \\
\text{CEG}_2 = \text{EB, ED, EL, EM, ES, GBP, VEAR} \quad \text{CEG}_2 = X \in X_2 \quad \text{CEG}_2 = 0.8 \quad \text{CEG}_2 = 0 \quad \text{Else} \\
\text{CEG}_3 = \text{IA, IB, IC, ID, IE, GIDOD, GO, VEPT, VEGW, VESB, VEST} \quad \text{CEG}_3 = X \in X_3 \quad \text{CEG}_3 = 0.08 \quad \text{CEG}_3 = 0 \quad \text{Else} \\
\text{CEG}_4 = \text{GBP, VEF, VELD, VEPT, GIDOD, GO} \quad \text{CEG}_4 = X \in X_4 \quad \text{CEG}_4 = 0.15 \quad \text{CEG}_4 = 0 \quad \text{Else} \\
\\
\delta = \begin{cases} 
1 & \text{Exposed} \\
0 & \text{Background} 
\end{cases}
\\
\text{Time adjustment factors:} \\
\beta_0 = 1 \\
\beta_1 = \begin{cases} 
1 & 1967 \leq T < 1995 \\
0 & \text{Else} 
\end{cases} \\
\beta_2 = \begin{cases} 
0.0037 & T \geq 1995 \\
1 & \text{Else} 
\end{cases} \\
\beta_3 = \begin{cases} 
1.75 & T \leq 1975 \\
1.25 & T > 1975 
\end{cases} \\
\beta_4 = \begin{cases} 
1.75 & T \leq 1981 \\
1.25 & T > 1981 
\end{cases} \\
\text{Exposure level (L) = CEL}_1 + \text{CEL}_2 + \text{CEL}_3 + \text{CEL}_4 \\
\text{Point estimate} = \delta \beta_0 \beta_1 \beta_2 \beta_3 \beta_4
\end{align*}
\]
### Mineral Oil MWF Exposure Intervals by Exposed Job Class and Time Period

<table>
<thead>
<tr>
<th>Mineral Oil MWF Exposure Interval, mg/m³</th>
<th>GBV, GB, GV, and GAF</th>
<th>EL, EM, ED, EB, ES, GIDOD, and VEAR</th>
<th>IC, ID, IE, EO, GBP, and GO</th>
<th>IB</th>
</tr>
</thead>
</table>

EB, exposed broaching; ED, exposed drilling; EL, exposed lathe; EM, exposed milling; EO, exposed other slow-moving operations; ES, exposed shaping; GAF, grinding airfoils; GB, grinding blades; GBP, grinding buff and polish; GBV, grinding blades and vanes; GO, grinding other; GIDOD, grinding internal diameter, outer diameter, and centerless; GV, grinding vanes; IB, intermittent exposed B; IC, intermittent exposed C; ID, intermittent exposed D; IE, intermittent exposed E; MWF, metalworking fluid; VEAR, various exposed all-around machining.
Specific Agent Results

Study levels similar to or less than professional practice recommendations.

Exposure Concentration by Year: Mineral Oil MWF

Hemeon 1955, 1963 = 15 mg/m³

1976 TLV = 5.0 mg/m³
Specific Agent Results

Study levels similar to or less than those published for other industries.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year</th>
<th>Task</th>
<th>Published Value</th>
<th>Highest study interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td>1978</td>
<td>Buff, polish, grind, weld (aircraft parts)</td>
<td>0.01 – 252 µg/m³</td>
<td>0.5 – 1.0 µg/m³</td>
</tr>
<tr>
<td>Chromium</td>
<td>1996</td>
<td>Saw blade grinding</td>
<td>1 – 12 µg/m³</td>
<td>0.005 – 0.01 µg/m³</td>
</tr>
<tr>
<td>Blue Haze</td>
<td>N/A</td>
<td>N/A</td>
<td>None reported</td>
<td>1000 – 5000 million particles/m³</td>
</tr>
</tbody>
</table>
Part/Process Methods

• Part and process analyzed to ensure any unsuspected agent that may be associated with a possible effect would not be missed
  – Estimated >3,000 agents over study period 1952-2001

• Used a screening method developed by Pierce & Esmen designed for complex exposure scenarios
  – Yields a reduced set for further in-depth investigation when an association between a set and health effect is detected

Part/Process Methods

• 20 part families determined with aid of P&W engineers
  – > 90 meeting hours with 95 engineers/experts
  – Selected “representative parts” for each family

• Processes abstracted from SOPs for representative parts and classified into 16 categories based upon:
  – Energy used in contaminant dispersion (thermal, mechanical, electrical, chemical)
  – Relative magnitude of air currents generated from energy form impacting contaminant dispersion
  – Type of contaminant evolved (particulate, fume, mist, vapor)
## Part/Process Methods

### Part Families
1. Baffles
2. Blades
3. Combustion chamber
4. Composites
5. Diffuser cases
6. Disks
7. Gearboxes
8. Gears
9. Hollow fan blades
10. Hubs
11. Integrally bladed rotors
12. Inlet cases/fans
13. Intermediate cases
14. Nozzle assembly
15. Seals
16. Shafts
17. Sheet metal fabrication
18. Stators
19. Tubes
20. Vanes

### Process Categories
1. Hot gas cutting
2. Hot machining
3. Hot joining
4. Hot curing
5. High airflow operations
6. Medium airflow operations
7. Low airflow operations
8. Very low airflow operations
9. Inspection and EDM
10. Hot dipping operations
11. Cleaning operations
12. Chemical surface treatment
13. Composite processes
14. Sheet metal processes
15. Facilities and Services
16. Limited manufacturing exposure

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Qualitative exposures (Yes/No) assigned to part/process job class and year
Exposure & Health Outcome

• An exposure in and of itself is not particularly meaningful or informative
  – It is relevant if there is a health effect demonstrated

• Agent-specific exposure estimates and part/process assignments provided to UPitt for use in their statistical analyses of exposures and health outcomes
Part 3a
Phase 3 Results
<table>
<thead>
<tr>
<th>Paper (Yr)</th>
<th>Study Component</th>
<th>Health Outcomes-Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>I -2008</td>
<td>Original Cohort Mortality Study (Phase 1)</td>
<td>CNS Neoplasms Deaths- Demographic</td>
</tr>
<tr>
<td>II – 2008</td>
<td>Original Cohort Mortality Study (Phase 1)</td>
<td>Non-CNS Deaths- Demographic</td>
</tr>
<tr>
<td>III – 2010</td>
<td>Original Cohort Incidence Study (Phase 2)</td>
<td>CNS Neoplasms Cases- Demographic</td>
</tr>
<tr>
<td>IV - 2010</td>
<td>Methodological</td>
<td>--</td>
</tr>
<tr>
<td>V- 2011</td>
<td>Methodological</td>
<td>--</td>
</tr>
<tr>
<td>VI- 2013</td>
<td>Updated Cohort Incidence Study (Phase 3)</td>
<td>CNS Neoplasms Cases- Exposure Classes</td>
</tr>
<tr>
<td>VII – 2013</td>
<td>Exposure Assessment– Methods &amp; Results</td>
<td>--</td>
</tr>
<tr>
<td>VIII - 2013</td>
<td>Updated Cohort Incidence Study (Phase 3)</td>
<td>Glioblastoma Incidence – Parts &amp; Processes</td>
</tr>
<tr>
<td>IX – 2013</td>
<td>Updated Cohort Mortality Study (Phase 3)</td>
<td>Non-CNS Deaths - Exposure, Parts &amp; Processes</td>
</tr>
<tr>
<td>Editorial-2013</td>
<td>Summary of Entire Study</td>
<td>All</td>
</tr>
</tbody>
</table>
Plant Group Comparisons: Glioblastoma Incidence Based on CT External Comparisons Slightly Elevated but Not Statistically Significant in North Haven

<table>
<thead>
<tr>
<th>Location</th>
<th>SIR-CT</th>
<th># = observed cases</th>
<th>() = number of workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Hartford</td>
<td>0.69</td>
<td>165 (136,616)</td>
<td></td>
</tr>
<tr>
<td>North Haven</td>
<td>1.07</td>
<td>55 (32,036)</td>
<td></td>
</tr>
<tr>
<td>Southington</td>
<td>0.97</td>
<td>29 (18,314)</td>
<td></td>
</tr>
<tr>
<td>Middletown</td>
<td>0.99</td>
<td>18 (14,726)</td>
<td></td>
</tr>
<tr>
<td>All Other</td>
<td>0.74</td>
<td>10 (9,092)</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant

# = observed cases
() = number of workers
Plant Group Comparisons: Glioblastoma Risk Based on Internal Comparisons Higher in North Haven, Southington and Middletown Compared with East Hartford

<table>
<thead>
<tr>
<th>Location</th>
<th>SIR</th>
<th>RR</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Hartford</td>
<td>1.00</td>
<td>1.00</td>
<td>165</td>
</tr>
<tr>
<td>North Haven</td>
<td>1.07</td>
<td>1.44</td>
<td>55</td>
</tr>
<tr>
<td>Southington</td>
<td>1.37</td>
<td>1.44</td>
<td>29</td>
</tr>
<tr>
<td>Middletown</td>
<td>1.44</td>
<td>1.44</td>
<td>18</td>
</tr>
<tr>
<td>All Other</td>
<td>0.69</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

Statistically significant

SIR-CT or RR
Exposure Analysis: Strategy

- Evaluated at **case-control and cohort level** (external and internal comparisons) and across all plants (exception: NH-blue haze)

- **11 exposure classes**: MWF-Min, MWF-Sol, nickel, cobalt, chromium, ionizing radiation, EMF, lead-cadmium, solvents, PCBs, blue haze (NH only)

- **4 metrics of exposure**: exposed/unexposed, duration of exposure, average intensity of exposure*, cumulative exposure*

- Results of 104 agent_exposure-response evaluations shown in published articles

* computed only for quantitative measures
Hypothetical Example of Positive Exposure-Response Relationship

Risk Measure (OR, RR, SIR)

Exposure Level

Increasing exposure leads to increasing risk

Baseline for risk measures = 1.0
Hypothetical Example of Null Exposure-Response Relationship

Increasing exposure does not lead to increasing risk

Baseline for risk measures = 1.0
Example: For All Workers, Glioblastoma Incidence Not Related to Cumulative Exposure to Metalworking Fluids

MWF-Min mg/m³-yrs

- Never exposed
- < 2.5
- 2.5 - 10.5
- 10.5 - 67.8
- 67.8+

OR - RR - SIR

Case-Control (OR)  
- Never exposed: 134 cases
- < 2.5: 36 cases
- 2.5 - 10.5: 36 cases
- 10.5 - 67.8: 36 cases
- 67.8+: 35 cases

Cohort-Internal (RR)  
- Never exposed: 127 cases
- < 2.5: 42 cases
- 2.5 - 10.5: 33 cases
- 10.5 - 67.8: 51 cases
- 67.8+: 24 cases

Cohort-External (SIR)  
- Never exposed: 127 cases
- < 2.5: 42 cases
- 2.5 - 10.5: 33 cases
- 10.5 - 67.8: 51 cases
- 67.8+: 24 cases

# = observed cases
Glioblastoma Incidence in North Haven Not Related to Blue Haze Exposure

Odds Ratio: case-control study

Blue haze exposure $10^6$ parts/m$^3$-yrs
- Green: Never exposed
- Purple: < 536
- Gray: 536 -
- Dark gray: 3116 -
- Blue: 19,110 +

# = observed cases

Elevations not statistically significant
Exposure Analysis: Summary

- In both the total incidence cohort and case-control studies, none of the chemical class metrics considered were associated with increased GB risk.

- GB incidence rates in NH were not related to workplace exposures, including the “blue haze” exposure unique to NH.
Work Experience Analysis: Strategy

- Used as a screening tool to identify possible workplace associations not otherwise feasible to examine (3,000+ chemical agents present in P&W work environment)

- Evaluated at case-control and cohort level (external and internal comparisons) and across all plants

- 20 part families and 16 process categories and 4 part x process combined groups

- Metric of exposure: Time spent in given category

- Results of 88 part, process and part x process evaluations shown in published article
Example: For All Workers, Glioblastoma Incidence Not Related to Time Spent Working with Blades

Odd Ratio or Relative Risk

Time Spent Working
- Never experienced
- < 1 year
- 1 - 4
- 5 - 9
- 10 +

# = observed cases

Elevations not statistically significant

Case-control Study
Incidence Cohort Study

218 16 22 8 13 225 36 6 7 3

P&W_Final - 42
Work Experience Analysis: Summary

In both the incidence cohort and case-control studies, none of the part families and/or process categories considered were associated with increased GB risk
Updated Cohort Mortality Analysis: Summary

- In Phase 1 mortality study, screening criteria (1.25-fold+ elevation in risk and statistically significant) applied (met criteria → evaluated further)

- Phase 1 screen identified kidney cancer and non-malignant respiratory disease but these were not related to factors examined

- Phase 3 screen based on updated data identified 2 COPD-related cause of death categories (original causes did not meet criteria)
  - Bronchitis, emphysema, asthma in Southington plant group
  - Emphysema in Middletown plant group

- COPD findings not related to relevant exposures (MWF - Min/Sol)

- Smoking or occupational exposure outside P&W cannot be ruled out as reasons for the COPD results; full evaluation limited by lack of smoking data for workers in study
Part 3b
Conclusions of Overall Study
Study Conclusions I

In the P&W plants studied, occupational exposures to chemical or physical agents decreased over the time frame of the study and quantitatively estimated levels were similar to or less than published data from other industries.

With the exception of elevated COPD-related mortality in two of five study plant groups, our evaluation of total and cause-specific mortality rates (excluding CNS neoplasms) found no evidence of elevated rates.

Smoking or occupational exposure outside P&W cannot be ruled out as reasons for the COPD results.
Overall Study Conclusions II

For CNS neoplasms, including GB, the results of our incidence study revealed no statistically significant elevations in overall rates among the P&W workforce compared with rates in the general populations of the U.S. and CT.

If not due to chance alone, the small to moderately elevated GB rates in NH may reflect unmeasured external occupational factors or non-occupational factors unique to NH or the baseline E. Hartford plant used in the internal comparisons.
What do the results mean?

Based on the results of our 12-year comprehensive investigation, we conclude that:

- The P&W workforce and their family members should be reassured that employment before 2002 at the P&W plants studied, including the NH plant, does not increase your risk of developing brain cancer and does not increase your risk of dying from any cause of death.
Acknowledgments

We gratefully acknowledge the support, cooperation and assistance of the following groups without whose help this study would not have been possible:

- The CT Department of Public Health
- The Scientific Advisory Committee
- P&W operators and HR, EH&S, engineering and management personnel
- The International Association of Machinists and Aerospace Workers (IAMAW)
- The Communications Facilitation Workgroup
Questions?