

SOLVING A MASSIVE WORKER

The largest workplace health study ever conducted is applying cutting-edge techniques to investigating an apparent cancer cluster—and highlighting the reasons why science doesn't always protect us at work • **By Carole Bass**

KEY CONCEPTS

- A seven-year investigation of brain cancer cases among Pratt & Whitney Aircraft workers in Connecticut has become the largest workplace health study ever performed, covering some quarter of a million employees over a span of 50 years.
- The study's massive scale has made data collection labor-intensive, but the size of the study population should also give the analyses power to detect even subtle patterns that might point to tumor causes, including previously unrecognized brain cancer triggers.
- More industrial epidemiology of this kind could improve worker health protections, many of which are extremely outdated. But funding and political support for such research are lacking.

—The Editors

In John Shea and John Greco's day, the cavernous Pratt & Whitney Aircraft plant was filled with an oily mist that sprayed from the grinding machines, coated the ceiling and covered the workers, who came home drenched in pungent machine oil. Degreasing pits, filled with solvent for cleaning the engine parts, dotted the factory floor; workers used squirt cans of solvent to clean their hands and clothes. Shea spent 34 years grinding engine blades and vanes at the million-square-foot facility in North Haven, Conn. In 1999, at age 56, he was diagnosed with brain cancer. Six months later Shea's friend and co-worker Greco learned he had the same disease: glioblastoma multiforme, the most aggressive type of brain tumor. A year after Shea's diagnosis, both men were dead, but their widows had already begun asking questions about the seemingly unusual number of cases of this deadly form of cancer at one of the world's top jet-engine manufacturers.

What began in 2001 as an investigation into an apparent cluster of brain cancers at North Haven—13 cases of primary malignant brain tumor among the workers, 11 of them glioblastoma, in just the previous decade—has turned into the largest workplace health study ever conducted. A team led by principal investigator Gary Marsh of the University of Pittsburgh and Nurtan Esmen of the University of Illinois at Chicago is engaged in painstaking detective work to solve a complex puzzle: first the researchers must trace an as yet undisclosed number of brain cancer cases among nearly 250,000 employees at eight Pratt & Whit-

ney plants over a span of 50 years and then determine, if possible, what might have caused the tumors by reconstructing workers' exposures to a slew of potentially toxic agents. The group expects to publish preliminary findings in the first half of 2008 and final results in 2009.

Marsh and Esmen's logistically daunting task illustrates the difficulty of such workplace epidemiology, involving multiple exposures at multiple facilities. The researchers' ability to provide concrete answers about what happened to Pratt & Whitney workers in the past will also be limited by incomplete scientific understanding, both of brain tumor triggers and of the toxicity of many chemicals used in industry. The Pratt & Whitney study, using the most sophisticated techniques available, could shed new light on both subjects. The investigation also underscores the fact that determining safe exposures to workplace toxics remains very much a problem of the present.

The National Institute for Occupational Safety and Health estimates that nearly 49,000 Americans die prematurely every year from work-related illnesses—more than eight times the number killed in on-the-job accidents. Most federal workplace exposure limits are based on science from the 1960s, however. As a result, newer Environmental Protection Agency guidelines for safe levels of a chemical in the air outside a factory can be as much as 45,000 times lower than regulations governing air inside the plant set by the Occupational Safety and Health Administration (OSHA). Politics and economics,

PHOTOGRAPH OF RUBIK'S CUBE BY JAMES PORTO; PHOTOILLUSTRATION BY JEN CHRISTIANSEN; BETTMANN/CORBIS (yellow); JAMES PORTO (blue); UNIVERSITY OF PITTSBURGH (red and orange); CONNECTICUT DEPARTMENT OF ENVIRONMENTAL PROTECTION (green)

HEALTH PUZZLE



rather than the limitations of science, may be the greatest barriers to updating those worker health protections. The Pratt & Whitney investigation therefore also illustrates how much better occupational epidemiology could be if the political will existed to bring the best modern science to the task of making workplaces safe.

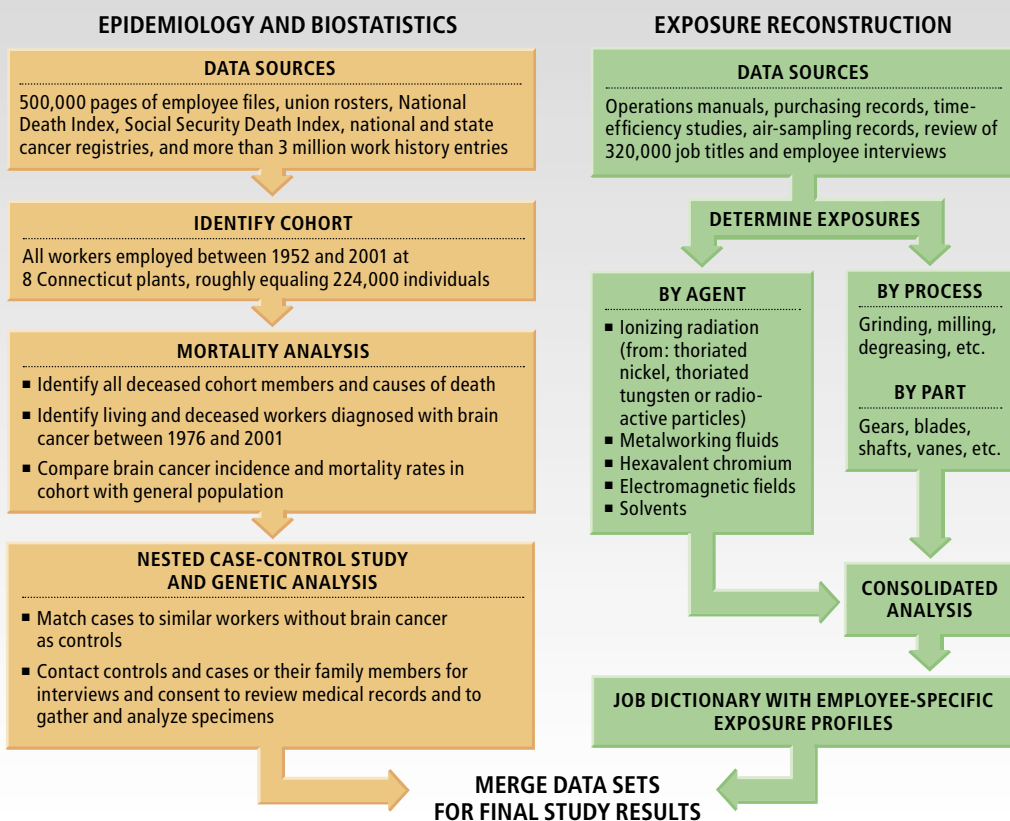
Amassing Evidence

When their husbands were diagnosed with the same rare tumor, Carol Shea and Kate Greco knew nothing about brain cancer or epidemiology. But it seemed an unlikely coincidence, so they started asking Pratt & Whitney for answers: How many other workers had brain cancer?

[EVIDENCE COLLECTION]

BUILDING THE DATABASES

To determine whether an unusual number of cases of brain cancer arose among Pratt & Whitney Aircraft workers and, if so, why, the investigators spent more than five years compiling enormous volumes of information about all of the company's Connecticut workers and manufacturing processes over a 50-year period. One of the two research teams set out to identify the study population, or cohort, and determine how many of that group developed brain cancer by sorting and tracing more than a quarter-million employee names. Meanwhile, the other team was culling a wide variety of sources to reconstruct what substances workers were exposed to between 1952 and 2001 in the course of doing their jobs.



Half a million pieces of paper illustrate the number of pages of employee records scanned by University of Pittsburgh researchers to compile worker lists and information.

JAMES PORTO

What might have caused it? By August 2001 a Connecticut Department of Public Health investigation found that the incidence in the preceding 10 years of glioblastoma among workers at the North Haven plant represented between 2.8 and seven times the expected rate, depending on assumptions.

At that point the state health department asked Pratt & Whitney, which declined to comment for this article, to hire an independent epidemiologist to investigate further. The company turned to Marsh, a biostatistician at Pitt's Graduate School of Public Health. Marsh specializes in what he calls "messy and labor-intensive" workplace health investigations, often involving tens of thousands of employees and multiple work sites. He immediately contacted Esmen, an expert in assessing and reconstructing workplace exposures, with whom he frequently collaborates.

The pair initially focused on the North Haven factory, which was shut down in 2002. But when they learned that the company did grinding work similar to the operations at North Haven in its main factory, in East Hartford, and different types of work at other Connecticut facilities, they decided to study all eight existing and defunct plants in the state. Thus, a study initially projected to cover about 100,000 employees grew to a \$12-million, seven-year investigation of close to a quarter of a million workers during the years 1952 to 2001.

The bigger project has two scientific advantages, Marsh explains: a higher statistical power, which reduces the chance of false negative results and increases the likelihood of detecting even subtle patterns; and better internal comparisons of work practices, exposures and health outcomes. Occupational epidemiology often suffers from the so-called healthy worker effect—misleadingly comparing disease rates among a group of workers with those of the general population, which includes people too sick

to work. Comparing subgroups of Pratt & Whitney workers with one another should produce a more accurate picture.

But the study's massive size also represents one of the researchers' greatest challenges. Working under project manager Jeanine Buchanich, Pitt employees and contractors spent a year on-site at Pratt & Whitney, scanning half a million pages of personnel records and abstracting them into a database of employee vital status information. Buchanich then began tracing the roughly 266,000 names—collectively known as the cohort—through national databases to see which employees had died and from what causes. A computer programmer wrote a protocol for sampling names from union membership rosters, which Buchanich checked against the cohort to see if people were missing. She also had to rectify database entries where the dates did not make sense: for example, where an employee was ostensibly hired before he was born or after he died. "The cohort file was fantastically clean," Buchanich says—with an error rate of less than 0.1 percent—"but it was still a couple hundred errors that you have to look up and resolve." After eliminating these and further refining the database, the cohort now comprises about 224,000 workers.

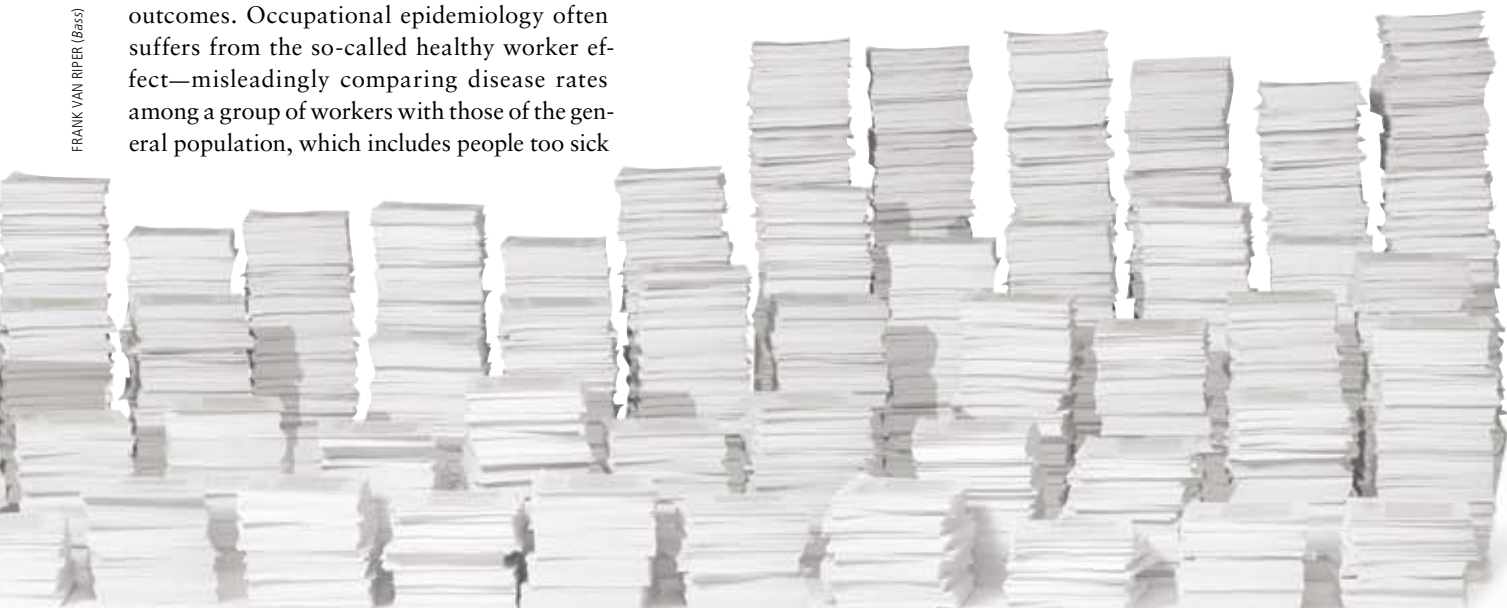
Meanwhile case manager Zb Bornemann has been hunting for brain cancer cases. He ran the entire cohort through the National Death Index and Social Security Death Index. And he continues to contact state cancer registries around the country, asking whether any names from the cohort match records of people with brain tumors. Where a match turns up, Bornemann tries to trace the next of kin through online databases. Some registries are a dead end. Some feel more

[THE AUTHOR]



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FRANK VAN RIPER (Bass)





WORKERS at Pratt & Whitney Aircraft's East Hartford plant prepare a jet engine developed for the Boeing 727 to be tested in July 1961. The factory is one of eight in Connecticut included in an investigation of brain cancer cases among the company's employees.

CANCER CLUSTER DEFINED

A seemingly unusual number of cancers occurring during a specific time period among people who live or work together can happen by chance. But an apparent cluster can also indicate that the illnesses have a common source. The mortality analysis portion of the Pratt & Whitney investigation will use statistical techniques "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 Connecticut 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."

like *Alice in Wonderland's* rabbit hole: in Washington State, Bornemann submitted six rounds of application materials for information about cancer patients, including one document that was rejected because it referred to the state cancer registry instead of the state department of health, which houses the cancer registry. Once Bornemann does locate a case's next of kin or, occasionally, a person living with brain cancer, he sends a letter asking for participation in the study: a phone interview, medical records and permission to analyze tissue from the person's brain tumor.

Finding cases factors into the first part of the study—the mortality analysis—which will determine whether a higher-than-expected rate of brain cancer or other diseases existed among Pratt & Whitney workers overall and among various subgroups. The second part is a nested case control study, in which investigators match each brain cancer case with a Pratt & Whitney employee of the same age, sex and year of hire in whom brain cancer did not develop. By com-

paring their medical and work histories, including the exposure assessment being developed by Esmen at U.I.C., the researchers hope to detect patterns that could explain why brain tumors occurred in some people but not in others.

In a third arm of the study, Pitt neuro-oncologist Frank Lieberman is looking at gene mutations in Pratt & Whitney employees' brain tumor tissue. If he finds a distinctive pattern, it could suggest that the Pratt & Whitney tumors were not random but shared some common causation.

Here some of the science is quite new. Lieberman is working with paraffin-embedded tumor tissue that has been stored for years at hospitals where Pratt & Whitney cancer patients underwent surgery. Until recently, that meant he would be limited to methods that allow only 15 to 20 genes per sample to be examined for changes known to be involved in tumor growth. Now, thanks to improved technology, he can also use microarray techniques previously available only for fresh tissue, which allow him to examine thousands of genes at a time, looking for small mutations as well as duplications or deletions of whole genes. "You can look for changes in patterns of [gene activity]," he says, "not just for changes up or down in specific genes."

Lieberman is comparing those profiles with a National Cancer Institute database and with brain tumor samples from patients at his Pitt clinic, as controls. "This is a very powerful technique," he states, in part because researchers "don't necessarily have to have a hypothesis at the beginning about which genes are important."

One of Lieberman's Pitt colleagues, Emanuela Taioli, uses similar molecular techniques to identify DNA damage caused by specific known carcinogens. The two groups are working together on a pilot effort to collect normal tissue from Pratt & Whitney workers with brain cancer; they hope to detect any molecular changes in that tissue and correlate them with carcinogens for which Esmen's team is finding exposures at Pratt & Whitney. In principle, those fingerprints of toxic substance exposure could represent early steps toward cancer. The science behind these strategies "is still very young," Lieberman cautions. "We're trying to use the opportunity that's presented by the enormous size and the sophistication of the epidemiology to get as much information about possible triggers for brain cancer as we can. But the techniques that are being used are, in a profound sense, still experimental themselves."

Industrial Archaeology

The work of Esmen's Chicago team is less experimental but just as monumental. The group has spent five years delving into Pratt & Whitney operations from the 1950s through the 1990s, trying to figure out what employees were exposed to and at what levels. "If the data is not there, it has to be reconstructed," says Esmen, a professor of environmental and occupational health sciences at U.I.C.'s School of Public Health. "It's almost like industrial archaeology."

The digging would be easier if the team knew what it was looking for. Scientists have long suspected an occupational source for some brain cancers. But the only proven cause is ionizing radiation, which a few Pratt & Whitney operations

did generate. Beyond that, the list of suspects comes from previous studies that found high rates of brain cancer among people who worked with certain metals, machine oils, and solvents but that have not been consistently replicated.

Working from Pratt & Whitney records, Esmen's team is boiling 320,000 job titles down to a manageable number of broader job categories. For each category, the researchers then try to quantify workers' exposure to the suspected agents during various time periods.

The numbers are only relative, though. "The important thing is to get things in the right order," Esmen says. If the researchers estimate a particular exposure was 10 units, "you don't know if it is really 6 or it is 12—but it's definitely

OSHA Lags Behind

"Understand this," says Roger Hancock, a member of the Pratt & Whitney study team: today's OSHA standards "were the latest toxicology data in 1968." He is not joking. OSHA opened shop in 1971 with a statutory mandate: "to assure so far as possible every working man and woman in the Nation safe and healthful working conditions." It adopted permissible exposure limits (PELs) for about 400 chemicals in one swoop, lifting them directly from voluntary industry standards. Those standards were developed by the nonprofit American Conference of Governmental Industrial Hygienists, or ACGIH, in 1968. During the rest of the 1970s, OSHA put together new exposure limits for nine other substances.

But in the next decade, the PEL express turned into a train wreck. In 1980 the U.S. Supreme Court struck down an OSHA standard that reduced the permissible level of benzene by an order of magnitude, saying the agency had to prove that its regulation would prevent a "significant risk of harm." Without defining "significant risk," the court suggested that one additional death for every 1,000 exposed workers was probably significant, whereas one in a billion was not. Ever since then, OSHA has viewed the one-in-1,000 number as the strictest possible standard. Some PELs allow much graver risks: for example, the 2006 limit for hexavalent chromium, issued under court order, corresponds to a cancer risk of 35 to 45 per 1,000, according to OSHA estimates.

In 1987 OSHA undertook a sweeping update of its limits for air contaminants. Less than two years later it issued PELs for 376 chemicals. More than half of those were tightened standards for substances on the original 1971 list; the rest were newly regulated substances. But industry and labor both challenged the law, and in 1992 a federal appeals court threw it out, ruling that OSHA had to carry out separate rulemaking procedures for each substance. It never did.

Despite the scientific difficulties, the ACGIH continues to crank out about 20 to 40 of its voluntary exposure limits, known as TLVs (for threshold limit values), every year. As a result, TLVs now cover more than 700 chemicals, compared with the 400-odd that OSHA regulates. "It's never-ending, because there's always more information," says Terry Gordon, who leads the TLV effort. "We're volunteers doing our best. If OSHA picked up the ball and ran with it, that'd be a great day."

In written responses to questions from *Scientific American*, OSHA em-

phasized that "updating an exposure limit is not a simple undertaking." Meeting the burdens imposed by Congress and the courts requires "extensive research" and "significant resources to adequately characterize the effect of revised PELs on employee health risks and to evaluate feasibility to ensure that revised standards are necessary, will be effective in protecting employees from health hazards in the workplace, and will be possible for employers to achieve." For hexavalent chromium, OSHA says it adopted "the lowest level that was feasible," based on "the totality of the evidence in the rulemaking record."

But OSHA could do far better, in the view of some who used to work there. Harry Ettinger, an industrial hygienist, led the Reagan-era effort to update the air contaminant limits. "It's an embarrassment" that most PELs still date from 1968, he exclaims. He sees the perfect as the enemy of the good. "I tried to convince labor that they were crazy to sue us. They wanted perfection. Perfection doesn't exist."

To another former OSHA official, Adam Finkel, the problem is priorities. "Most people who know what they're talking about would agree that occupational health [accounts for] 80 to 90 percent" of work-related deaths, says Finkel, who was the agency's director of health standards from 1995 to 2000. Yet "the emphasis has always been on safety" rather than health. He himself was forced from his job after calling attention to on-the-job health hazards facing OSHA's own inspectors; the agency eventually agreed to a six-figure settlement of his whistle-blower claim. Far from taming a perfectionist streak, he believes, "the agency just has to catch up to late 20th-century science. There are so many single agents that we know workers are exposed to at 1,000 times higher than they should be." With so much low-hanging fruit, Finkel says, OSHA's top priority should be "old-style industrial hygiene."

In any case, the "extensive research" and "significant resources" that OSHA states are necessary to update worker health protections have to come from somewhere. More often than not, the industrial interests that would be subject to those regulations are the ones paying for the studies. On the workplace health front, the National Institute for Occupational Safety and Health's research budget has been flat or declining. And manufacturers have not only fought governmental regulation; they have also taken the independent ACGIH to court, trying to block it from releasing its nonbinding exposure limits.

—C.B.

FAST FACTS

- On average, nearly 16 workers die from injuries sustained at work and 134 die from work-related diseases in the U.S. every day.
- An estimated 11,500 private-sector workers have a nonfatal work-related injury or illness every day.
- 9,000 workers are treated in emergency rooms because of occupational injuries every day.

SOURCE: National Institute for Occupational Safety and Health

not 100.” Because no measurements exist, the researchers extrapolate from interviews with factory workers and engineers. They also use mounds of company-supplied data, such as purchasing records (for quantities of materials used), 1970s time-efficiency studies (for length of time spent on any given task), internal publications with esoteric titles like *A Versatile Engineering and Manufacturing Capability*, and whatever air sampling Pratt & Whitney may have done over the years.

That last information source might sound like a rich lode for exposure reconstruction. But it is trickier than it seems, Esmen points out. An epidemiologist trying to assess exposures across the entire workforce would take random samples from each work group and document changes from shift to shift or day to day. An industrial hygienist called in to fix a problem—respiratory complaints, for example—would sample only the “problem” area and would consider only the highest levels registered of a suspect substance.

Industrial hygiene textbooks instruct future practitioners to take a full range of samples, says researcher Steve Lacey, who teaches these techniques to U.I.C. graduate students. “But that’s not the reality.” Roger Hancock, another team member who spent a quarter of a century practicing industrial hygiene in the private sector,

knows the reality: “You arrive at a plant with a luggage cart full of [testing] equipment, and you have a week. Maybe they’re running that process once that week, so you have one chance to take that sample. If the highest sample is below concern, then you don’t take any more samples.”

“Below concern,” for most companies, means legal compliance. If a workplace meets OSHA standards, that is good enough. But academic researchers and medical textbooks recognize that what is good enough for OSHA is not always good enough to protect workers’ health [see box on preceding page].

Determining safe exposure limits is not easy, acknowledges Terry Gordon, who chairs the American Conference of Governmental Industrial Hygienists committee that issues voluntary exposure limits for chemicals. Like OSHA, his group of about 20 volunteers does not conduct original research but rather relies on published studies. Animal toxicology investigations, with their controlled lab conditions, are tidier than the murky epidemiology of real people exposed to unknown amounts and combinations of various substances, both on and off the job. But the clarity of animal studies is also a weakness: they measure the effect of one chemical at a time, whereas workplaces typically contain multiple toxicants. “Human data is always preferable to toxicology,”

PHOTOGRAPH OF MONITOR BY JAMES PORTO; PHOTOILLUSTRATION BY JEN CHRISTIANSEN; UNIVERSITY OF PITTSBURGH (tumor samples)

[ANALYSIS]

INTERPRETING THE DATA



With the consent of affected workers or their families, the investigators obtained tumor samples and, in some cases, normal tissue, to examine for signs of DNA damage that could have been caused by carcinogens (left). When they combine those results with information about what substances employees were exposed to, and when (right), they hope to reveal whether on-the-job exposures contributed to the cancers.

GENETIC CLUES

Changes, or mutations, in DNA isolated from tumor samples like those shown on the computer screen can hint at what triggered the tumor.

- A distinctive pattern of mutations in the tumors of different workers could suggest a common causation, for example.
- Such analyses can also determine the duration of cumulative change and even the order in which changes occurred, to help pinpoint when cancer growth might have started.
- Certain known carcinogens damage DNA in specific ways, leaving a fingerprint of exposure in tumor cells and even normal tissue.
- Mutations in genes for carcinogen-metabolizing enzymes are another category of cancer-promoting changes detectable in noncancerous tissue that could help explain how a tumor was initiated.

VISUALIZING EXPOSURES

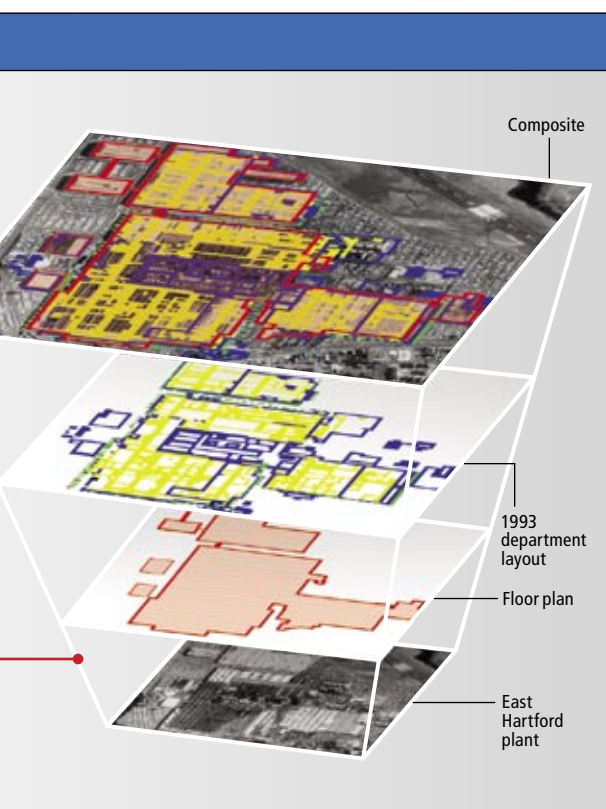
To manage the enormous amount of data the investigators gathered about the factories’ operations between 1952 and 2001, they created a “geographic information system.” The database allows them to retrieve and connect data about the locations of employees, parts and processes—and, hence, worker exposures to potentially toxic agents—at different times during the study period.

says Gordon, a professor and researcher in New York University's department of environmental medicine. But "with human data, there's often not enough exposure data, and the exposure information is often not linked to health effects."

The Pratt & Whitney researchers are doing their best to avoid those pitfalls, but they recognize some of the elements that make this study "messy," as Marsh puts it. Because Bornemann has incomplete information from state cancer registries, he will likely miss brain cancer cases. Of those he has located, only 41 percent have agreed to participate; Marsh wants at least 60 percent to assure scientific validity. Marsh also notes that while participants' recollections about medical history and lifestyle are "reasonably good at a broader level, it breaks down when you get to any level of detail." And the U.I.C. team's exposure reconstruction, for all its thoroughness, will still be an estimate of what happened decades ago on shop floors that have since been shuttered or drastically cleaned up.

A Start in the Right Direction

After seven years and \$12 million, there is a good chance the Pratt & Whitney study will wind up like so many other workplace health investigations: inconclusive. Researchers say the phenomenon stems from the difficulty of the science.



Like all epidemiology studies, this one can at best prove associations between exposures and health effects, not strict causation. It is especially hard to detect causes of diseases like cancer, which typically shows up decades after the offending exposure. And finding a definitively safe level of exposure to carcinogens can be impossible.

Many researchers might love to have \$12 million for studies that could produce clearer results in less time, but Pratt & Whitney's millions would probably not otherwise have been spent on workplace health research. Even if the study never provides conclusive answers to all the questions it raises, the effort will hardly have been a waste of time or money.

For starters, there is the prospect of some kind of answers for the Pratt & Whitney families. "I've been involved in this project since the day it started," says Pitt project manager Buchanich. "That we're finally going to be able to tell these workers something—it's been a long time."

Regardless of the specific outcomes, the project might be able to tell the rest of us something as well. The mounds of new data it is generating could help unravel the complexities of multiple toxic exposures and could contribute, in Lieberman's words, to understanding "the basic biology of how brain tumors get started." In addition, the study's unprecedented scope is spurring new techniques for managing the massive amount of information. The U.I.C. team, for example, is building a geographic information system, or GIS, database that will let team members map factory operations across time and space. Such technology could be useful for any study in which spatial relations are important, such as archaeology or industrial engineering, according to Esmen.

So this archaeological foray into Connecticut's industrial past may yield tools and information to help workers and brain cancer patients in the future. In doing so, it could help lower the scientific barriers that stand between Americans and healthy workplaces. Reducing the nonscientific barriers will require a different set of tools.

"The largest preventable health and safety risks remaining to be addressed in our society occur disproportionately in U.S. workplaces," wrote Adam Finkel, a former OSHA health standards director, in a letter last May to Representative Lynn Woolsey of California, who chairs the House Subcommittee on Workforce Protections. "The solution is not to complain about the need to do good science but simply to get back to doing good science, like OSHA used to do." ■

MORE TO EXPLORE

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