

CATCHING



A KILLER

How UTMB researchers helped to finger butadiene as a probable human carcinogen and reduce the permissible workplace standard for the chemical by a thousand-fold

BY JUDIE L. KINONEN

UTMB Professor of Environmental Toxicology Jonathan Ward was on his office phone when he spotted the killer's fingerprint. It was 1992, and Ward was scribbling down numbers relayed to him by a colleague who had tested urine samples from workers at a synthetic-rubber plant in Port Neches, Texas, to determine how much of a chemical called 1,3 butadiene they had been exposed to. In front of him lay the results of an assay run by UTMB Adjunct Assistant Professor Marinel Ammenheuser, showing the amount of genetic damage—mutations—in each worker's white blood cells. As he wrote down the data on exposure next to the data on genetic damage, he stopped suddenly and grabbed a piece of graph paper.

"I plotted out those two sets of numbers and thought, 'There's correlation here,'" says Ward, his calm demeanor broken slightly by the memory. As soon as he got off the line, he rushed out to find Ammenheuser. For months, the then-sixty-year-old grandmother had been peering into a microscope, painstakingly counting damaged cells sorted out by an assay she had fine-tuned to detect mutations in a single specific "reporter" gene. Suddenly, her persistence had been rewarded.

"A lot of science is, frankly, rather boring, but once in a while you just get something that works," Ammenheuser recalls, smiling broadly. "It was really quite exciting."

A correlation between butadiene and genetic mutations meant a possible link between butadiene and cancer, which often arises from damage to genetic material. Before Ammenheuser's and Ward's study, butadiene had been connected to cancer only by suspicions and anecdotal evidence, hotly debated epidemiological research, and strangely contradictory animal studies. Although synthetic-rubber workers had long suspected that butadiene exposure was responsible for all sorts of so-called hematopoietic cancers—cancers of the blood, including leukemia, lymphoma, and Hodgkins disease—the limited evidence was inconclusive, and workplace exposure to the chemical remained all but unregulated by the federal government.

Epidemiological data suggested that very high exposures in the early years of synthetic-rubber manufacturing posed a cancer risk. Now, though, there were numbers, quantitative evidence that plant workers exposed

Two years before he was scheduled to retire, Bodie Pryor learned he had leukemia—and began to ask why he and so many fellow workers in synthetic rubber plants were developing it.

to current levels of butadiene were three times more likely to suffer genetic mutation than their non-exposed colleagues. Those numbers had come from a small-scale study run on a shoestring budget provided by a tiny foundation funded by Port Neches rubber workers. But they would mark a turning point in a debate that had begun more than two decades before—a struggle between an industry and its employees, fought on the contested ground of science. And in the end, the numbers would make a difference.

ORANGE, TEXAS, 1976

Bodie Pryor just wasn't feeling well. At about noon every day, the fifty-nine-year-old manager of a polyethylene plant in Orange, Texas, would muster the last of his strength to lock his office doors and stack his day's paperwork in piles on the floor. Then he'd climb up on top of his desk for a long, restless nap. Pryor was only two years from retirement at the time and for about a year had chalked up his fatigue to old age. But then it finally dawned on him that something more was wrong.

When a Houston doctor wrapped his arm around Pryor's shoulder to tell him he had leukemia, Pryor couldn't even feign surprise. He had seen this before. In his time in the chemical industry—particularly the thirteen years he had spent at the giant synthetic-rubber plant complex near Beaumont in Port Neches—he had known a lot of people who had gotten leukemia.

Too many, he thought.

When he had the energy, Pryor began quietly collecting the names of rubber-plant workers who either had leukemia or had died from it. He stopped counting when he got to forty—more than enough cases to confirm his belief that there was a connection between synthetic-rubber production and leukemia.

He had a hunch about what that connection was, too: butadiene.

Butadiene is essential in the rubber industry, making up 70 percent of the finished product in items like tires. It's also incredibly reactive and has to be stored under high pressure at low temperature in special spherical tanks. Back when Pryor was diagnosed with leukemia, everyone in the rubber business knew butadiene was extremely flammable and had to be handled with care, but exposure to the chemical was all but unregulated in the workplace. The Occupational Safety and Health Administration (OSHA) had set the permissible exposure limit (PEL) for butadiene at 1,000 parts per million (ppm) “to prevent narcosis and irritation,” it said. By comparison, known carcinogens like benzene and styrene had much lower PELs—100 ppm for styrene and

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In addition to Pryor, one of those few was a man Pryor contacted not long after beginning the research that eventually led him to file a lawsuit against his former employers in 1979—the first to be filed by an individual claiming butadiene was responsible for his leukemia. Gene Rasheta was the financial officer for the Oil Chemical and Atomic Workers International Union (OCAW) local in Port Neches, which is now a part of the Paper, Allied-Industrial, Chemical and Energy Union (PACE). A long-time resident of that community, Rasheta knew virtually all of the two-thousand-plus OCAW union members by their first names. As their officer, he kept close tabs on their injuries and illnesses and tracked their health after retirement. For some time he had been worried about how often he seemed to be hearing about workers with leukemia. He reasoned that a chemical used in the plants might be responsible, and butadiene—ubiquitous, highly reactive, hardly regulated butadiene—seemed the most likely suspect.

Rasheta had shared his concerns with Dr. Marvin Legator, then director of the Division of Environmental Toxicology at UTMB's Department of Preventive Medicine and Community Health. Legator agreed that butadiene's safety was worth worrying about—particularly for Texans. Nine of the twenty-two U.S. synthetic rubber plants are in Texas, and three-quarters of the nation's butadiene is produced and used in Texas. When Pryor enlisted Beaumont attorneys William Townsley and Dale Hanks to file his butadiene-exposure lawsuit, Legator agreed to serve as an expert witness in the case. He also testified on behalf of others who brought suit after Pryor claiming butadiene had made them victims of hematopoietic cancers—plant workers and their survivors, citizens of Port Neches who lived near the plants, and alumni of Port Neches High School (which for years stood adjacent to a synthetic-rubber plant).

In his testimony, Legator presented the scientific evidence tying butadiene to leukemia. When the case was filed, the faintly damning data consisted primarily of a small epidemiological study conducted at Port Neches by the National Institute of Occupational Safety and Health (NIOSH). It showed a weakly positive correlation between butadiene exposure and leukemia risk. But the industry-sponsored International Institute of Synthetic Rubber Producers (IISRP) was determined not to allow Pryor's case to establish a precedent linking butadiene to leukemia. It commissioned a large, industry-wide epidemiological study conducted by Genevieve Matanoski of Johns Hopkins University. Matanoski's report generally raised no leukemia concerns, except for



Marinel M. Ammenheuser adapted a sensitive new test that let her calculate the amount of genetic damage in workers' white blood cells.

black workers, who often worked closest to butadiene. It seemed like good news for the industry, as did an industry-funded rat study in the early 1980s that found no significant correlation.

Then a mouse study in 1983 raised some eyebrows. The research had to be abandoned halfway through, because leukemia had already claimed one-third of the mice exposed to butadiene. (The debate still rages about which model—rat or mouse—is most appropriate in predicting the effects of butadiene on human beings.)

Amid this conflict, Matanoski followed up her original report with what's called a nested, case-controlled epidemiological study—one separating those workers with the highest butadiene exposure from those with the lowest. Her new findings meant the end of her working relationship with the IISRP: deaths by leukemia, Matanoski reported, were seven to nine times more common among workers with the highest butadiene exposure than among those with no exposure.

The IISRP hired one scientist after another to refute Matanoski's findings. Their strongest contention was that the report was powerless to predict health risks for *today's* workers. By its nature, an epidemiological study

would be influenced by the effects of exposures to butadiene that existed in plants in the 1940s and 1950s—exposures that were, arguably, much higher than modern-day plants would allow. Rubber plants today are much cleaner, the IISRP contended, and safety standards are much higher.

Still, the IISRP could not take all the sting out of Matanoski's study. She defended her work, claiming that despite its focus on the past, her report did demonstrate that exposed workers had a higher relative risk of leukemia. Along with some convincing animal research, her data got the attention of the EPA and of OSHA, which in the mid-1980s began to consider lowering the PEL for butadiene.

'TOO DUMB TO KNOW WHAT WE WERE DEALING WITH....'

Meanwhile, the scientific uncertainty had been the undoing of Bodie Pryor's butadiene suit. Pryor finally settled out of court in the late 1980s for an undisclosed sum. In the record books, the cause of his leukemia was listed as styrene. Pryor and his lawyers, Townsley and Hanks, say now they know better.

"We were just too dumb to know what we were dealing with back then," Hanks said. "The science just wasn't there to support a butadiene case."

Townsley, Hanks, and Legator knew what the science lacked, what a judge and jury needed to hear—not data from epidemiology or animal research, but a reputable study correlating current workplace butadiene exposures in humans with cancer risk. UTMB had scientists who could do the investigation, and Legator was eager for a chance to get his colleagues to work on the problem.

So Townsley approached his friend Gene Rasheta with an idea for creating a scientific research foundation. Rasheta could find plant workers with established claims and ask if they would be willing to assign a small percentage of their claims to a foundation for butadiene research. If they agreed, Townsley and Hanks would try their cases at a reduced fee.

After wrangling for non-profit status with the Internal Revenue Service, Townsley got a charter for what ultimately would be called the Workplace Toxics Foundation. His "grandiose plan" for the foundation, he says jokingly, was that other lawyers in the area would contribute, too. That never happened.

Still, after about a year, through Townsley's and Hanks's contributions alone, the foundation amassed \$25,000. Legator and his team at the Department of Pre-

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ventive Medicine and Community Health gladly accepted it, and Ammenheuser and Ward went to work. Their goal was to measure damage to the workers' genetic material using a technique known as an autoradiographic mutation assay, which had proven quite useful to Ammenheuser for detecting DNA damage in lymphocytes (white blood cells) of tobacco smokers and people exposed to chemotherapy and radiation.

Although earlier studies had failed to find butadiene-related chromosome damage, Ammenheuser and her colleagues suspected that the assays they used might not have been sensitive enough. So she refined the mutation assay technique for the butadiene study, homing in on a single gene called *HPRT*—a "reporter" gene that had been found to be a good indicator that other genes had suffered mutation as well.

Because it was so limited in scope, no one expected groundbreaking news from the investigation. Running the assay was incredibly labor-intensive, and the initial study was limited to fourteen plant workers and five control subjects recruited at UTMB. Yet the correlation between butadiene exposure and genetic damage that Ward

first noted that afternoon in 1992 was so striking that it brought UTMB national attention, leading to \$3.5 million in federal grants to date for butadiene research, with Legator as the initial principal investigator and Ward assuming that role later. And one year later, when OSHA decided to lower the butadiene PEL from 1,000 to 1 ppm, it cited UTMB's tiny Port Neches study as contributing crucial evidence that even current exposures to butadiene might be enough to cause genetic damage that could lead to cancer.

DISCOVERING 'GOOD' AND 'BAD' DETOXIFIERS

Ammenheuser and Ward's report had implications that went beyond a simple relationship between butadiene exposure and genetic mutation. Not long after they published their findings in *Environmental Health Perspectives*, UTMB researcher Sherif Abdel-Rahman followed up on what seemed to be a confounding factor in the data: some of the subjects—even those with the highest exposure to butadiene—had very few genetic mutations, while some of those exposed to smaller amounts of the chemical had a relatively high number of mutations.

Supported by a hefty grant from the National Institutes of Health with Ward as principal investigator, Abdel-Rahman—who had joined the team that conducted the original study—led an effort to explain the disparity. His group found that workers who seemed virtually unharmed by exposure to butadiene were “good detoxifiers.” When the chemical enters a cell, a “good detoxifier” has a powerful line of defense—a gene responsible for turning out a particular enzyme that metabolizes the chemical and renders it harmless. For the least susceptible workers in the study, that important gene does its job very well.

“Why don't all cigarette smokers develop lung cancer?” Abdel-Rahman asks. “Our research shows that if you are a good detoxifier, you won't have as high a frequency of mutation as a bad detoxifier.” A “bad detoxifier,” the team found, might suffer genetic damage at the tiniest exposure levels—measured not in parts per million, but parts per *billion*.

This new information has profound implications, both inside and outside the plant fence. Can plants keep their exposure levels for toxic chemicals low enough for even their most sensitive employees—the “worst detoxifiers”? Or should prospective workers be tested for susceptibility before they are hired?

And what about those living and working nearby? Even if a plant keeps its emissions below recommended



Chasing the causes of cancer: Sherif Abdel-Rahman, Jonathan Ward, and Marvin Legator.

standards, some highly susceptible individuals still may suffer genetic damage that could lead to cancer.

'I'M GOING TO LIVE TO SEE THIS THROUGH.'

Bodie Pryor is now eighty-seven. His longevity has astounded doctors. But Pryor says there must be a good reason he's still here. He recalls his depositions in 1979, when attorneys representing his former employers were testing his patience. “I told them, ‘You think you can drag this thing out until I die, but that's not going to happen. I'm going to live to see this through!’”

Pryor keeps close tabs on current UTMB research undertaken by Abdel-Rahman, Ammenheuser, Legator, and Ward. He's especially concerned now with airborne exposure to chemicals in his community, and he's an outspoken proponent of more stringent emission controls. Riding through the streets of Port Neches, Pryor points, visibly agitated, toward the maze of billowing pipes off the road, then toward the school a couple of blocks away. He says that some days the plant emissions get so heavy the kids can't go outside for physical education classes. But today the skies look clear enough, as high school boys in shorts and shin pads practice soccer; the girls pass by in clusters, ponytails bouncing, jogging toward the track.

Watching them, Pryor's grey eyes are tearing, his voice tight. “The plants build these high chain-link fences, but they can't keep that stuff in,” he says. “They can't build fences high enough.” ❏