The Murky World of Toxicity Testing

Four scientists are on trial for fraud in a case that has cast doubt on the safety of 200 pesticides and on EPA's monitoring procedures

Chicago. Four scientists are being tried here on criminal charges that they faked studies on drugs and chemicals during the 1970's when they ran a major private laboratory, Industrial Bio-Test Inc. (IBT) of Northbrook, Illinois. The government has taken a hard line in this case for two reasons.

Before its collapse, IBT was one of the most prestigious contract labs in the country, with around 22,000 studies to its credit, the basis for safe product ratings for hundreds of drugs and pesticides. In addition to being prominent, IBT seems to have been uncooperative. The Food and Drug Administration (FDA) and the U.S. Attorney's office charge that IBT's top scientists were so deeply mired in the scandal that they resisted a federal investigation in 1976 and plotted to hide evidence of their cheating.

The trial began on 13 April in the U.S. District Court in Chicago and has been crawling along ever since. It may not be over until September. The pace is set by the defendants and their battery of nine expert criminal lawyers. The leader is a prominent Chicagoan, George Cotsirilos, who recently represented a Teamsters Union official in a notorious pension fund case. His law firm says its top rate is $150 an hour, per lawyer.

In this trial Cotsirilos represents Joseph C. Calandra, the founder and ex-president of IBT, also a professor of pathology at Northwestern University since 1942. The other defendants are Moreno Keplinger, a Fulbright scholar and former general manager of the Northbrook lab; Paul Wright, a former toxicology department head at IBT now employed by Monsanto; and James Plank, Keplinger's former assistant. They are charged with mail fraud: passing phony data to the government and calling it scientific information.

Each defendant has his own lawyers, but the fees are being paid by IBT. The company is just a shell of its former self. Its chief reason for existing now is to minimize damage to its parent, the Nalco Chemical Company. Calandra sold IBT to Nalco 17 years ago, long before this trouble arose, and remained president until shortly after the federal investigation began in 1976. He left in March 1977.

The current president of IBT, Yvonne Bonahoom, says the firm is paying legal bills on the understanding that employees who carry out company business in good faith must be indemnified. However, she says that IBT's continued support depends on what comes out in the trial. She would not elaborate.

Nalco has set aside a multimillion-dollar reserve to take care of IBT's problems. One reason for doing so is that IBT's former clients are thinking of filing civil damage suits. These would be strengthened by a criminal conviction in the current trial. IBT has already settled seven civil suits and is helping former clients dig through the IBT archives to salvage what they can of old test data.

> Even IBT's wealthiest clients, such as Monsanto, Inc., are still digging out from the rubble.

The defendants see the government's case as an exaggeration of some minor slip-ups that occurred a very long time ago. But one reason there has been delay is that the defendants have fought hard for it. Two years passed between the indictment and the trial. At one point the court had to evaluate Cotsirilos's claim that his client's aneurism of the aorta made him too weak to stand trial. In the end, Calandra was judged strong enough. Even now, hardly a day passes when Cotsirilos does not move for a mistrial. As for the significance of the data fudging, suffice it to note that it has called into question the safety reviews of more than 200 pesticides, many of which are being retested at great expense by the manufacturers. Even IBT's wealthiest clients—such as Monsanto, Inc., which claims to have spent $12 million replacing bad IBT studies—are still digging out from the rubble.

The John Dean of this case is a pudgy technical report writer named Philip Smith. As the government's lead witness he testified steadily from 5 to 19 May, enduring a sustained probe by the defense aimed at finding flaws in his character as well as his story. Smith showed remarkable self-control. One attorney complained acidly that Smith, who shattered more than one theatrical drum-roll of defense queries with a plea to repeat the question because of poor hearing, seemed less deaf in cross examination than in direct testimony. But the witness was not shaken.

Smith's testimony is critical because he had an overview of all that went wrong. After the FDA began investigating in April 1976, Calandra put Smith in charge of an in-house audit. Smith told the jury that he was asked to find out where all the problems were and summarize them in a private report to Calandra, left untyped to avoid showing it to the secretaries. Smith provoked an angry protest from the defense when he said that after this report was finished, he felt "threatened" by Calandra. Indeed, the "threats" seem mild, but reveal something about the atmosphere at IBT.

Late in 1976, according to Smith, after Nalco learned that there was trouble at IBT and decided to send an investigator, Calandra urged Smith not to confess anything that he was not "100 percent sure of," and to consider 95 percent certainty as inadequate. Calandra also allegedly told Smith he would deny this conversation had taken place. In early 1977 after Smith talked to the Nalco agent, Smith claims that Calandra "suggested I might be subject to charges of libel for things I believed were true and for things I was telling him." Calandra left in March 1977. Three months later Smith was fired and given 20 minutes to clean out his office. When confronted by Justice Department investigators the next year, Smith invoked the Fifth Amendment against self-incrimination, was given immunity, and became a paid government witness. Much of the defense's interrogation has been aimed not at the substance of the charges but at suggesting that Smith is the kind of person who might be bullied into making up stories about his boss. But the government plans to substantiate Smith's ac-

count with testimony from other IBT staffers, including one who will testify about the shredding of data, another who will state that raw data cited in two studies never existed, and one who will say that his findings of a health effect were arbitrarily deleted from a report.

Although there were dozens of cases to choose from, the government decided to prosecute on studies of just four compounds: an antibacterial agent used in "deodorant soap" (TCC), an arthritis drug (Naprosyn), a pesticide (Nemacur), and a herbicide (Sencor). All have been retested and found reasonably safe.

Adrian Gross, the former FDA investigator who launched this case with a visit to IBT in April 1976, says that his suspicions were aroused by the fact that IBT's data were "unbelievably clean," proving the safety of products a little too convincingly. Going over some of IBT's raw data, Gross saw a term he had not come across before. "TBD, TBD, I kept seeing it and I wondered, what the hell is this?" Gross recalls. It stood for "too badly decomposed," meaning that test animals had died and rotted in their cages before yielding any data. The total breakdown of animal care at IBT, well described in a recent article by Keith Schneider,* is an important part of the prosecution's argument.

TCC is a Monsanto antibacterial agent which the company hoped to prove safe enough to add to bath soap in larger quantities than the FDA had allowed before. Rats in a long-term (24-month) study in 1971 were being fed various quantities of TCC to learn at what levels of exposure the compound would cause atrophy of the testicles. The room where the rats lived came to be known as "the swamp" because it housed a $120,000 automatic watering and cleaning machine, a new gadget that never worked properly. Bits of feed and feces clogged the water nozzles and drain hoses, drenching some animals in a cold spray while others died of thirst. In these foul conditions, the mortality rate was high, 80 percent by one estimate. But according to the prosecution, IBT's report on TCC did not reflect the premature deaths or the fact that dead rats were replaced with many healthy ones which had not been fed the same test chemical.

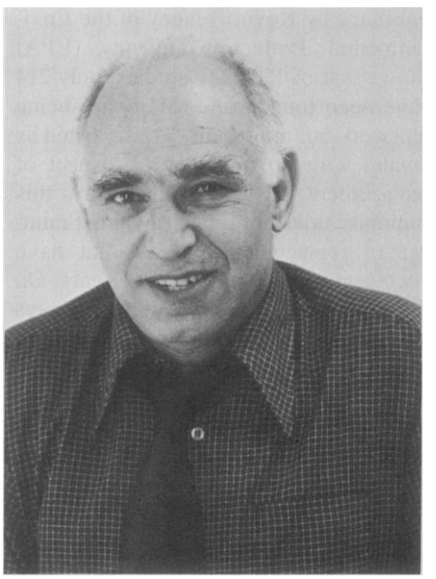
The government also claims that Calandra ordered an important change in a pathologist's report on TCC, making it seem less hazardous. Donovan Gordon, IBT's former pathologist, has become a government witness and is expected to say that he found evidence that TCC was affecting the testis at the lowest dose being given, but that Calandra ordered him to interpret the tissue slides differently, finding no effect.

A particularly sensitive question is the degree to which Monsanto was aware of what was happening. It arises because Paul Wright, who originally came from Monsanto, helped run the TCC study while at IBT for 18 months, then returned to Monsanto at a higher level and oversaw the report's drafting and publication. Monsanto denies any complicity and declines to comment on Wright. Wright's attorney said during the trial that it is "amazing" to charge that Wright would defraud his own employer by faking a report on TCC. Just the opposite, the attorney said, Wright kept his Monsanto superiors "well informed" of all aspects of the study.

Jeff Lowenthal—Newsweek

Joseph Calandra

Ran IBT from 1952 to 1977.



Adrian Gross

Found IBT's data too clean to be true.

While the government is not exploring Monsanto's involvement, the trial inevitably touches the company. Already, an exchange of letters between Calandra and Monsanto's manager of toxicology in 1975 has become public, revealing that the company at least once did tell IBT how to express its findings. The case involves Aroclor 1254, a compound containing PCB's, not a part of the trial. Monsanto had IBT change the wording on a report from "slightly tumorigenic" to "does not appear to be carcinogenic." It was done, a spokesman says, to ensure that all reports on Aroclor were phrased consistently.

Three other products cited by the prosecution had problems similar to TCC's. The government charges that the Nemacur and Sencor studies were cut short because they were running past the deadline, and that the last 4 months' data were fabricated. In addition, the government says that the positive control mice which were supposed to get tumors did not, so Keplinger lifted tumor data from a study at another lab and used them instead. Smith testified that in doing this, Keplinger transformed skin-painting data into feeding data, figuring that the former would convert roughly to a feeding rate of 1 part per 1000.

In the case of Naprosyn, the government charges that all the final blood and urine data were fabricated, because no blood and urine samples were collected. The government also claims that an appendix on gross pathological observations was entirely invented. The animals had died and been thrown out before it was written. Evidence has been introduced indicating that Smith would not include these false data in the Naprosyn report, but was tricked into signing his name on another piece of paper, which was attached later.

IBT grew from obscurity in 1952 to a huge multistate laboratory in the 1970's. It seemed to have a knack for making chemicals come out clean in tests. The prosecution is working on the assumption that IBT was greedy, taking on too much with too little expertise. In the late 1960's, as a new environmental consciousness awakened in the nation, federal regulators demanded more laboratory proof that chemicals were safe. IBT leapt at the opportunity, not knowing how to fulfill its commitments.

Smith testified that in the early 1970's he recalls that there were only seven

*"Faking It: The Case Against Industrial Bio-Test Laboratories," in the Spring 1983 issue of *The Amicus Journal*, published by the Natural Resources Defense Council, New York, N.Y.

technicians to take care of 10,000 to 15,000 rodents, each of which was supposed to be monitored individually. When Calandra quit, IBT had a business backlog of $25 million. By then, management controls and staff morale had broken down. The company collapsed from within.

After the fiasco became known, the U.S. and Canadian governments jointly began reviewing all compounds that relied on IBT studies for marketing approval. The few affected drugs have been cleared, but the record on pesticides is not as good. A summary prepared in February by Kevin Keaney of the Environmental Protection Agency (EPA) shows that of 1205 key studies, only 214 have been found valid. Many are being replaced, but at present, 737 are listed as invalid with no immediate prospect of replacement. Other officials say this summary does not reflect the great number of replacement studies that have been sent to EPA in the last 2 years. On the other hand, Keaney's summary says nothing about the quality of long-term toxicological studies supporting the IBT problem pesticides. Ninety-five percent of these studies are very poor, according to an official with first-hand knowledge. The first full report on all of this is expected in "mid-June," according to EPA.

Federal laboratory inspectors agree that the cheating they found at IBT was in a class by itself. After Senator Edward Kennedy (D–Mass.) held hearings on these problems, Congress passed a Good Laboratory Practices Act in 1978. The two responsible agencies (EPA and FDA) began an inspection program to prevent future IBT's from happening. The new regulations have driven marginal labs out of the market, in particular, out of the complex business of running long-term studies. A couple of firms withdrew only after being hit with criminal indictments, similar to the one in Chicago. An experienced lab watcher at EPA says that no other company since then has tried to grow as rapidly in as many areas as IBT. Today, any outfit that seems to build momentum quickly is watched.

Despite the attention this issue has received, one EPA official concedes, there are still three or four testing centers that have a record of submitting sloppy work or of losing data. They are seen as living in a kind of limbo. EPA has not yet decided how it should regard the work they did in the past in support of pesticide registrations. It is a knotty problem, and one EPA is unlikely to solve by mid-June.—**ELIOT MARSHALL**

Clinch River Supporters Pin Hopes on Baker

Supporters of the Clinch River Breeder Reactor are once again pinning their hopes on the powers of persuasion of Senate Majority Leader Howard Baker (R–Tenn.). Unless Baker can persuade the Senate to vote funds for the reactor, the project will be dead. In the last 2 years, it has been approved by the Senate by a single vote.

The fate of the breeder has been placed in the hands of Baker and the Senate by a tactical move on the part of the House Committee on Appropriations. Rather than risk having the project shot down on the House floor, the committee deleted all funds for the reactor from the Department of Energy's appropriations bill. The House version of the bill will thus contain no funds for the reactor, and it will then be up to the Senate to keep the project alive.

The thinking is that if the Senate approves funds for the reactor, the House members of the conference committee—who will be mostly breeder supporters—will simply go along with the Senate's action. But if the project is shot down on the House floor, the House conference committee members would have to vote against the project.

In the past, Baker, in whose state the reactor would be built, has been instrumental in steering the project through the Senate. But Baker recently announced that he will not seek reelection. As a lame duck, his powers of persuasion may be reduced.

—**COLIN NORMAN**

The Reascendancy of Edward Teller (contd.)

Edward Teller has seen his influence in Washington and his standing in the scientific community wax and wane over the years, but now, at age 75, he is again riding high. His protégé, George Keyworth II, is installed as President Reagan's science adviser, and Teller was recently influential in persuading Reagan to push for a space-based antiballistic missile system. Then, on 24 May, Reagan awarded Teller, along with 11 other scientists, the National Medal of Science, the nation's most prestigious scientific award. The other recipients were:

Philip W. Anderson (physicist) of Bell Labs and Princeton University.

Seymour Benzer (geneticist) of the California Institute of Technology.

Glenn Burton (agricultural scientist) of the U.S. Department of Agriculture.

Mildred Cohn (biophysicist) of the University of Pennsylvania.

F. Albert Cotton (chemist) of Texas A & M University.

Edward Heinemenn (aeronautical engineer) of Heinemann Associates.

Donald Katz (chemical engineer) of the University of Michigan.

Yoichiro Nambu (physicist) of the University of Chicago.

Marshall Stone (mathematician) of the University of Massachusetts.

Gilbert Stork (chemist) of Columbia University.

Charles H. Townes (physicist) of the University of California at Berkeley.—**COLIN NORMAN**

House Appropriations Committee Axes NCAM

Nobody can accuse the House Appropriations Committee of being consistent. On 24 May, it voted to delete all funding for the National Center for Advanced Materials (NCAM) from the Department of Energy's budget request, on the grounds that the proposal to build the facility has not been adequately reviewed. Then, in the same breath, the committee approved $5 million apiece for new research facilities at Catholic and Columbia universities, even though those facilities have had even less review than NCAM (*Science*, 3 June, p. 1024).

The committee complained that the NCAM proposal was added to DOE's budget request by the White House, and was thus not given "the customary and desirable peer review" by the scientific community. NCAM has been vigorously promoted by George Keyworth, President Reagan's science adviser, but last month, 100 scientists wrote to the House Committee on Science and Technology to complain of the lack of input from the