Agent Orange Study Hits Brick Wall

After using new blood sera tests, CDC concludes neither military records nor the self-assessments of veterans are reliable guides to past exposure to dioxin

In 1967 and 1968 an area of South Vietnam known as the III Corps tactical zone saw the war's heaviest spraying of the defoliant Agent Orange. So it was from the III Corps region that epidemiologists with the Centers for Disease Control (CDC) hoped to find subjects for a congressionally mandated study on the health effects of exposure to dioxin, or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the compound that contaminated Agent Orange during the herbicide's manufacture.

The search party appears to have run into an epidemiological brick wall. CDC has concluded that military records were not written with number-crunchers in mind. Nor are the self-assessments of veterans a reliable guide for identifying people with high levels of exposure to Agent Orange.

What this means is that finding large numbers of exposed veterans for a broad-based epidemiological study would be both difficult and expensive, if not impossible. In recent weeks, CDC has made the rounds in Washington, delivering the politically charged news at a 6 August meeting of the science panel of the White House's Agent Orange Working Group and before a 27 August meeting of the long-running Agent Orange Advisory Panel, which serves the congressional Office of Technology Assessment (OTA).

It is news that will certainly disappoint and anger many veterans who believe that dioxin-laced Agent Orange is responsible for a litany of health woes. Dioxin has been found to be highly toxic for some species of laboratory animals, but the link to disease in humans is still not known.

CDC came to its conclusions after testing blood sera from "exposed" veterans stationed in the III Corps area between 1967 and 1968 against a control group of veterans who served stateside and in Germany during the same years. Both groups' sera contained the same low levels of dioxin. It was a finding that took many by surprise, as it rubs against the popular belief that Vietnam veterans were literally drenched by the herbicide.

The history of CDC's Agent Orange Study is one in which science and politics are intertwined. Under pressure from veterans' groups, Congress in 1979 passed a law calling for a large-scale epidemiological study on the health effects of dioxin exposure. Originally, the Veterans Administration (VA) was handed the job, but it was transferred to CDC because it was believed to be the more impartial agency (the VA has refused to compensate veterans who claim their poor health is caused by exposure to dioxin).

Working with the U.S. Army and the Joint Services Environmental Support Group, CDC came up with what it thought was a valid design for the study. Veterans would be scored for exposure to Agent Orange based on a system of "hits," or the number of times a ground soldier's company was within 2 kilometers of a recorded spraying that had been applied within the previous 6 days. Veterans with high and low exposure scores would then be rounded up and compared to an unexposed control group. Or at least that was the general idea.

UPI/Bettmann Archive

Spraying in Vietnam. *Twenty years later, exposure levels cannot be determined.*

But the advisory panels and even CDC were concerned that military records might not be sufficient for identifying individual ground soldiers who had come into contact with Agent Orange. One problem is the nature of military records themselves, which range from the exceptional to the nonexistent, says Richard Christian, director of the Joint Services Environmental Support Group, the agency responsible for feeding data to CDC. Military records detail the comings and goings of companies of 150 to 200 men, not smaller units, and certainly not individual soldiers, who during the melee of war can be just about anywhere. Platoons of a dozen men, for example, were often as far as 20 kilometers from company headquarters. "You have to remember that records management was not a top priority at the time. Killing the enemy was," says Christian.

If this were not a big enough obstacle for CDC's epidemiologists, another was added. Christian's agency confirmed earlier suspicions by concluding that herbicide spraying was grossly underreported. CDC had assumed that it could base its calculations of exposure by tracking the spraying done by the U.S. Air Force, which kept detailed notes of its aerial "Ranch Hand" spray missions. According to Robert Worth, chief scientist for the centers' Agent Orange Projects, CDC failed to grasp the ubiquitous use of Agent Orange in Vietnam, where it was routinely sprayed not only from airplanes, but from helicopters, as well as off the backs of trucks and men. Many of these ad hoc spraying missions never found their way into the records. Says Christian: "You got to thinking there was a hell of a lot more spraying going on than we knew about."

To confirm that the records of troop dispersal and spraying were insufficient for identifying subjects for a large epidemiological study, CDC in 1986 offered to do the current validation study, which compares the levels of dioxin in blood sera to military records and veterans' self-assessments of exposure. The recently devised test is a great improvement over the old, which required a surgical biopsy of 10 grams of fat taken from a subject's abdomen or buttock. The new test requires that only blood be drawn; lipids contained in the serum are screened for dioxin. Using stored blood from the Air Force, CDC found that dioxin has a half-life in humans of approximately 7 years, meaning that high levels of exposure in Vietnam would still be detectable in sera today. But at about $1000 each, the test is not cheap.

To date, 573 veteran ground soldiers from four battalions operating in the III Corps region have visited the Lovelace Foundation Medical Clinic in Albuquerque, New Mexico, to have their blood drawn. Of the Vietnam veterans screened, 25% told CDC they had either been present during spraying of Agent Orange or handled spraying equipment. Another 70% of the Vietnam veterans said they had been indirectly exposed to Agent Orange—by marching through a defoliated jungle, for example. A control group of 88 veterans who did not serve in Vietnam, but were on duty in 1967 and 1968, have also been tested. Only 6% of these men reported exposure to the herbicide.

The results: both groups' median dioxin levels were 3.8 parts per trillion, which is about the ambient level of dioxin one would expect to find in citizens of industrialized countries. In addition, there was no association between a veteran's self-assessment of exposure to the herbicide and elevated levels of dioxin in his serum.

Originally CDC's team feared that it would not be able to find enough Vietnam veterans with low exposure to dioxin to serve as a control group. What they appear to have found is the exact opposite: though spraying of Agent Orange was apparently widespread in Vietnam, it is extremely difficult to find substantial numbers of veterans with high exposure.

What happens now? Says Vernon Houk, director of the Center for Environmental Health at CDC: "I don't think you need a road map to get to the position where you conclude that you can't do a scientifically valid study." According to CDC's Worth, his group is at a loss to design a more valid protocol. "We took our best shot," he says.

The advisory panels appear to agree that a broad-based epidemiological study may not be possible. "I'll say it again: We need to abandon this craziness of trying to do these huge longitudinal studies based on military records or the self-perceptions of vets," says Lewis Kuller, an epidemiologist at the University of Pittsburgh and a member of OTA's advisory panel. Neal Castagnoli, a toxicologist at the University of California at San Francisco and also a member of OTA's Agent Orange panel, says, "TCDD was something for the veterans to grab hold of. It is so toxic for some lab animals. But we're just not seeing the problems we might have expected. And we're not seeing the huge levels of exposure, either. Did we make a mistake focusing on TCDD and not some other materials?"

Other studies on the health effects of the Vietnam war are in progress. The CDC is looking at selected cancers of veterans and is

"We need to abandon this craziness of trying to do these [kinds of] longitudinal studies."

continuing its large Vietnam Experience Study, which has shown greater mortality rates for Vietnam veterans in the first 5 years after service, deaths due mainly to automobile accidents, suicides, homicides, and drug poisonings. The Air Force continues to track its Ranch Handers, the teams that sprayed Agent Orange from aircraft. The National Institute for Occupational Safety and Health is looking at civilians exposed to dioxin during its manufacture. On 3 September the VA released details of a sweeping mortality report that found Marine ground troops had a 58% higher rate of death from lung cancer than expected and a 110% higher rate of death from non-Hodgkin's lymphomas. Similar rates of cancer death, though, were not found for Army veterans. The VA report stated that although Agent Orange exposure may be a suspect, the study did not investigate possible etiological factors, which could also include antimalarial drugs, viruses, cigarette smoking, and other herbicides besides Agent Orange.

Whether these studies are enough to satisfy the veterans is doubtful. Frustrated with CDC's efforts, the New Jersey State Agent Orange Commission is working with Peter Kahn, a biochemist from Rutgers University in New Brunswick, New Jersey, who believes the problem with the CDC study lies in the pool of veterans examined. Kahn is now gathering a small group of veterans who served in the III Corps region. He believes that if epidemiologists ask the right questions, they can find veterans who experienced high levels of exposure. His study, though, has only just begun.

Wayne Wilson, the director of the New Jersey commission and a veteran who saw two tours of duty in Vietnam, expressed the frustration felt by many of his peers: "I don't know much about all the scientific mumbo-jumbo, but you're not going to tell me these guys can't find vets who've been exposed to Agent Orange." At present, that is exactly what CDC is telling veterans like Wayne Wilson. ■ **WILLIAM BOOTH**

MSU Faults Strobel for Dutch Elm Test

A Montana State University committee has concluded that the bacterial strain Gary Strobel released in his controversial field test is not a recombinant DNA product and thus National Institutes of Health (NIH) guidelines "likely do not apply." However, Strobel clearly violated Environmental Protection Agency (EPA) regulations by testing a genetically modified microbial pesticide without prior approval, the committee found. In response, MSU president William Tietz reprimanded Strobel on 2 September and required that his future field experiments be reviewed by the department and his university's biosafety committee.

Since Strobel injected 14 elm trees on campus with a modified strain of *Pseudomonas syringae* designed to prevent Dutch elm disease, the question of whether this is a recombinant organism—and which regulations he violated—has been the subject of considerable debate (*Science*, 4 September, p. 1097). NIH guidelines apply only to recombinant DNA products; EPA rules cover a broader class of genetically modified products. Strobel maintains that because this is not a recombinant organism, he did not need NIH or biosafety committee approval. He admits to knowingly violating EPA regulations—EPA has imposed mild sanctions on him—but claims that federal regulations are confusing and inconsistent.

The committee faulted Strobel for his ignorance of federal regulations, claiming that it "constituted material failure to comply with university policy." Without addressing whether biosafety committee approval was required, Tietz said, "If there is *any* question of applicability of rules and guidelines . . . prudent action directs faculty members to the committee." But Tietz also expressed hope that the incident will increase "awareness of the tangled interpretations, definitions, procedures, exceptions, inclusions and classifications that dominate today's biotechnological research."

The university's biosafety commitee is now investigating another field test of a genetically modified bacterium that Strobel conducted in California, Montana, South Dakota, and Nebraska in 1983 and 1984. Preliminary information suggests that this strain of *Rhizobium meliloti* is not a recombinant DNA product, says Clifford Bond of the biosafety committee. EPA is not investigating the test because it occurred before the agency adopted its biotechnology policy in 1986. Meanwhile, on 3 September, in what he hopes will be the final episode in this saga, Strobel cut down the 14 elm trees. He leaves next week for several months in Europe. ■ **LESLIE ROBERTS**