

JULY 1989

TESTIMONY OF HELLEN GELBAND, SENIOR ASSOCIATE
OFFICE OF TECHNOLOGY ASSESSMENT
U.S. CONGRESS
SUBMITTED TO THE U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

Update on Agent Orange Exposure in Vietnam and Related Studies

July 10, 1989

Just over a year ago, I testified before this subcommittee on what was known about exposure to Agent Orange in Vietnam. Summarizing briefly, men whose jobs regularly involved handling herbicides--Air Force Ranch Hands and chemical corpsmen, mainly--had exposures high enough to result in persistent elevated body burdens of dioxin. Other men, including some infantrymen, probably had occasional direct exposures when spraying around bases with backpack or truck-mounted sprayers. Most ground troops, however, probably had relatively little exposure. When Congress mandated an Agent Orange study in 1979, and for several years thereafter, this was not the commonly held view. Initially, the biggest design problem for the study was thought to be identifying enough men who had been in Vietnam and were unexposed to serve as a comparison group for the many thought to have been exposed heavily to Agent Orange. Only after several years of painstaking research in the military records, and finally, measurements of blood dioxin levels in veterans, did an altered picture emerge. Research completed in the last year has tended to confirm the validity of blood dioxin levels as a marker for heavy exposure in the past.

The field is not without controversy, however. The most prominent claim that the scenario above does not accurately portray exposure to Agent Orange comes from the American Legion. Their dissent is based their own study, which they believe demonstrates that a large proportion of Vietnam veterans had significant exposure to Agent Orange, and that those exposures are associated with a number of current serious health conditions. OTA reviewed the American Legion study in January 1989 at the request of the House and Senate Veterans'

JULY 1989

Affairs committees. We believe that major flaws in the design of the study preclude the conclusions that the American Legion has drawn about exposure to Agent Orange and other herbicides and about subsequent health effects.

Information will continue to come in from studies of Vietnam veterans and from other populations with known dioxin exposure. In the past year, new information on exposure has come from the Ranch Hand Study and from preliminary results of a National Institute for Occupational Safety and Health (NIOSH) study of former production workers exposed to 2,3,7,8-TCDD ("dioxin"). After describing these developments briefly, I will review the studies still in progress, including the Air Force Health Study (the "Ranch Hand Study"); the Selected Cancers Study, being conducted by the Centers for Disease Control (CDC); and the Department of Veterans Affairs (DVA) Proportionate Mortality Study. After that, I will discuss some problems of the American Legion study, particularly relating to the herbicide exposure assessment used, and comment on a recent report updating mortality data for the population around Seveso, Italy, a site of heavy dioxin contamination from an explosion in 1976.

New Information on Exposure to Dioxin

Over the past year, blood from Ranch Hand Study participants (see below for details of the study) was drawn and forwarded to CDC for analysis, which is nearly completed. The results to date show consistently elevated levels of dioxin in Ranch Hands who had the greatest direct contact with herbicides--e.g., men who operated spray equipment in the air and those who cleaned out airplane spray tanks on the ground--and "background" levels (for the U.S. population, "background" is currently considered to be less than about 20 ppt) in those with little or no direct contact. When all the analyses are in, the Air Force plans to reanalyze the 1987 examination results using these blood dioxin levels (and levels extrapolated back to Vietnam service), which should give a more precise estimate of the relationship of health effects and exposure than has been possible previously. The reanalysis should be finished in 1991.

NIOSH has been studying workers employed between 1951 and 1972 in the manufacture of chemicals known to have been contaminated with dioxin. The 281 workers and 260 non-worker comparison participants were examined for a wide range of physical effects and had blood drawn for dioxin analysis. The workers had been employed at two plants, one in New Jersey and one in Missouri, and had worked for varying lengths of time; the comparisons were matched by sex, age, and race, and came from the same communities as the workers. NIOSH researchers have reported on dioxin levels analyzed thus far, comprising 27 workers and 19 comparisons from New Jersey. The average dioxin level in the workers' blood was 208.2 parts per trillion (ppt); the average for the comparisons was 8.2 ppt, far lower than the workers. Overall, the exposures of these chemical production workers took place earlier than the period of heaviest use in Vietnam (1967-69). The mean end date for workers was 1964, with an average of 4.2 years of exposure (including only days actually worked in production). Within the exposed group, dioxin levels were highly correlated with the length of exposure. Workers with exposures of about two months or less had levels similar to the comparisons (below about 20 ppt), and those with years of exposure ranged up to 717 ppt. In one anomalous case, a worker with 462 days of documented exposure had a unexpectedly low level, 12.2 ppt. Also, a receptionist, assumed to have had no exposure during her two years at the plant, had a slightly higher than expected level of 26.1 ppt (the other receptionist in the study, who had been employed about 15 months, had a level of 11 ppt). Analysis of physical examination findings by levels of dioxin has not yet been completed.

Ongoing Studies

Ranch Hand Study

The approximately 1,200 participants in Operation Ranch Hand, the Air Force fixed wing aircraft program responsible for most Agent Orange spraying, form the largest identifiable group of veterans known to have had significant exposure to the herbicide. The Air Force has

been studying these men and a group of Air Force Vietnam veteran "controls," matched by military occupation and other pertinent characteristics, since 1982, when they conducted their first analysis of Ranch Hand deaths since the war and the first in a series of interviews and physical examinations. Since then, the analysis of causes of death has been updated periodically, the most recent report appearing in April 1989, based on the 74 Ranch Hand deaths that have occurred. Analyses of physical examinations conducted in 1982 and 1985 have been released, and analysis of a 1987 examination is, according to the Air Force, progressing on schedule for release in the first quarter of 1990. Future physical examinations are scheduled for 1992, 1997, and finally, 2002. An additional report, a complete analysis of birth outcomes based on birth certificates and medical records, is nearly complete and should be released in early 1990, according to the Air Force.

Because of the relatively small number of Ranch Handers, and the fact that they are generally middle-aged and healthy, relatively few (epidemiologically speaking) instances of serious disease and few deaths have occurred. The strength of this study is in assessing the possible effects of Agent Orange on diseases that occur more commonly, and also on more subtle, subclinical conditions that may be detected in the extensive laboratory testing that has been part of the study.

Currently and at least for the next few years, it will be impossible to draw any conclusions from the Ranch Hand Study about Agent Orange and cancer, unless there is a dramatic increase in cancers over what has been seen so far. The evidence to date does not suggest an excess of cancers, but the number of cases is too small to rule out a small or moderate increase.

Selected Cancers Study

The Selected Cancers Study is one of three studies originally proposed by CDC to fulfill the mandates of PL 96-151 and 97-72. (The other two are the Vietnam Experience Study (VES), completed in 1988, and the Agent Orange Study, which proved infeasible.) Because cancers are relatively rare in middle age, the predominant age group of Vietnam veterans, CDC sought to test hypotheses related to Vietnam service and certain specific cancers in a case-control study, a more efficient means of studying rare diseases than is the cohort approach of the VES. Like the VES, however, the "exposure" is to what has been called the "Vietnam experience," and not to Agent Orange. Blood dioxin measurements are not part of this study. (The test had not yet been developed when the study began, and it is uncertain whether blood dioxin determinations in people who already have cancer would be valid, in any case).

If the Selected Cancers Study reveals that having served in Vietnam puts men at a higher risk for developing the cancers under study--soft-tissue sarcoma, lymphoma (including Hodgkin's Disease and non-Hodgkin's lymphomas), nasal and nasopharyngeal cancers, and primary liver cancer--it will be impossible to know whether Agent Orange might be the cause. In the case of primary liver cancer and nasal and nasopharyngeal cancers, in fact, other causes would be more likely suspects. It is known for certain that chronic hepatitis B infection is responsible for most primary liver cancer around the world. This cancer is relatively rare in the United States, but it is the most prevalent cancer in Asia, where a large percentage of the population is infected with the hepatitis B virus. In the Selected Cancers Study, no evidence of past or present hepatitis B infection is available for cases or controls, so infection with it cannot be evaluated as a risk factor. The VES did assess hepatitis B, however, and reported that Vietnam veterans had a significantly higher prevalence (14.1%) of past exposure (though not chronic) than did non-Vietnam veterans (11.1%).

The idea that some nasopharyngeal cancers may have a viral etiology has been suggested by the worldwide distribution of these cancers and other evidence. The Selected Cancers Study will not have the information to assess this possibility.

The power of the Selected Cancers Study to detect an association with Vietnam service is very good for soft tissue sarcoma and lymphoma, and somewhat lower, but still good, for primary liver cancer and nasal and nasopharyngeal cancers. This good power is based on an assumption that all veterans were exposed to the particular aspect of the Vietnam experience that might be important in causing cancer. If a cancer-causing element of the Vietnam experience were less than ubiquitous, however, the power of the study would be diluted accordingly. It is worth emphasizing, though, that the power of the study is best for soft-tissue sarcomas and lymphomas, the cancers most frequently implicated as associated with phenoxy herbicides.

According to CDC, the full report of the Selected Cancers Study is scheduled for release in spring 1990. Initial analytic problems resulting from AIDS-related lymphomas among the cases have apparently been resolved to the investigators' satisfaction.

DVA Proportionate Mortality Study

The DVA proportionate mortality study was discussed at length at this subcommittee's hearing last June. The clearest findings that provided cause for concern were the excess deaths among Vietnam veterans (compared with Vietnam era veterans who served elsewhere) from motor vehicle accidents, accidental poisonings (including drug overdoses), and other accidents and injuries. Two other findings, however, became the focus of discussion and debate: excess deaths from non-Hodgkin's lymphoma (NHL) and lung cancer among Marine Vietnam veterans. Both of these findings were based on relatively small numbers, but suggested the need for

JULY 1989

followup. As I testified last year, the most likely cause of the excess lung cancer deaths is a difference in smoking rates between the two groups. The NHL excess might suggest the presence of an unidentified risk factor limited to Marines, or could be a chance finding.

During the past year, DVA have continued work on this study and undertook specific followup studies on the Marine findings. First, the entire proportionate mortality study has been updated to include deaths that occurred in 1982-84, adding about 11,000 to the original 50,000 earlier deaths. Second, deaths among Army veterans who served in I Corps, where most of the Marines served, have been analyzed separately to see whether the Marine findings applied generally to other men who served in the same part of Vietnam. Third, DVA has conducted a case-control study of NHL and Hodgkin's Disease, selecting cases and controls from the DVA patient treatment file. DVA researchers recently reported at a scientific meeting that no association was found between Vietnam service and these cancers, but no written report of the study is yet available for review. Lastly, DVA is conducting a separate study of Marines, comparing deaths in a cohort of about 10,000 Vietnam veterans to 10,000 Vietnam era veterans. According to DVA, the first three of these efforts should be completed relatively soon, and the Marine mortality study should be completed in about a year. These are all important studies and their results will be of great interest.

NIOSH Dioxin Registry Studies

Results from the NIOSH study of workers from the New Jersey and Missouri plants, mentioned above, will be coming in over the next two years. CDC has now completed most of the dioxin blood assays, and data from the physical examinations are being analyzed by biological system. According to NIOSH, dioxin levels for the complete study cohort, and reports on three biological systems should be finished in fall 1989, with publication in early

1990. A separate part of the study consists of an analysis of birth outcomes to all members of the cohort. This has required collecting hospital and vital statistics records for all births, a time consuming procedure. That part of the study will probably not be completed until 1991.

NIOSH also has been studying the causes of death among all workers in the dioxin registry. About 7,000 production workers with potential dioxin exposure comprise the registry, and in the neighborhood of 20 percent of them are deceased. A rough index of exposure (number of days worked with the possibility of direct exposure) for each worker has been derived from personnel records from each plant. Based on the early results from the New Jersey plant (described above), time exposed appears to correlate relatively well with current dioxin levels, and therefore, with actual past exposure. This study should be completed in late 1989 and published in 1990.

The American Legion Study

The American Legion sponsored a study to examine the health, social, and economic consequences of service in Southeast Asia (SEA). A sample of their members who had served during the Vietnam era were asked to fill out questionnaires concerning their military experiences and aspects of their subsequent functioning and wellbeing. The study was conducted by researchers based at the Columbia University School of Public Health, and the results appeared in five papers published in the December 1988 issue of Environmental Research.

The investigators reported deficits in a number of social, economic, physical, and psychological measures that they related to having served in SEA. They also reported that among SEA veterans, problems appeared to be associated with more extensive reported combat experience, and with having higher scores on an Agent Orange exposure estimate scale. OTA formally reviewed this study in January 1989, at the request of this Committee and the Senate Veterans' Affairs Committee. My testimony is based on that review.

JULY 1989

The American Legion study has major flaws that call into question the validity of the findings reported, particularly those related to herbicide exposure. These flaws include: 1) aspects of the method of selecting the study population and low rate of response to the questionnaire, both of which may have contributed to a lack of comparability of SEA and non-SEA veterans in the study, and possibly lack of comparability of subgroups of SEA veterans (e.g., men who believed they were exposed to herbicides or who were in heavier combat and who have health problems may have been more likely to participate than other men); 2) an unvalidated and probably invalid method for assessing Agent Orange exposure; and 3) an unvalidated and probably invalid approach to collecting health (and possibly other) information about the participants. All epidemiologic studies suffer from some bias, and no methodology is perfect. However, the American Legion study has such serious problems that, even though some of its conclusions might be correct, the evidence produced by the study cannot be relied upon for an understanding of the consequences of having served in SEA during the Vietnam era. Each of the major problem areas is discussed in detail in OTA's January 1989 review. In my testimony, I will speak mainly about problems with the method used to estimate herbicide exposure.

Agent Orange Exposure Estimation Method

The method used to arrive at numeric Agent Orange (and other herbicide) exposure scores for individual participants is described in a 1986 paper by Stellman and Stellman. As have previous attempts at developing an Agent Orange exposure index, this one combines information from soldiers' locations and the computerized records of herbicide spraying (from the HERBS and Services HERBS tapes), taking into account time and distance from spraying. The authors make a number of claims for this methodology, the most general being that it "can be profitably used in most epidemiologic studies of the effects of herbicides on U.S. troops." Further, that "the accuracy and precision of the method are comparable to, or exceed, those

used in many major environmental and occupational studies." They state that "a sizable number of individuals were classified as 'high' exposure," and that the data "make the convincing point that sufficient numbers of troops are available and identifiable for epidemiologic study of herbicide effects."

The American Legion exposure estimation method suffers from more severe problems than did CDC's best attempt at an exposure index, which was ultimately rejected as inadequate.

The most serious of the problems with the American Legion exposure estimation method are:

1. **Self-reported location data:** Nearly 20 years after the fact, veterans were asked to recall each location at which they spent time during their tour of duty in Vietnam. Especially for men who moved around frequently (probably those in combat), this is an almost impossible feat.
2. **Locations were chosen from a list of place names provided in the questionnaire.** While men might have been near a particular town, large U.S. bases, where many men were stationed, and where combat troops were likely to have been, were not in the middle of towns. The place names may refer to places many miles off, yet it was presumably these actual towns that the American Legion researchers used as points of "location," from which the distances to spray coordinates were calculated. It is impossible to judge the accuracy of this method, and the investigators provide no information to support their claim that the method is "precise and accurate." In fact, it appears to be far less precise than CDC's method of using grid coordinates from military records of troop locations.
3. **There is no discussion of missing data, yet there must have been significant gaps in the information reported on the questionnaires.** If gaps were ignored, as seems likely, it is possible that reporting a lot of places or accounting for a greater percentage of the tour of duty would produce higher scores. This is one point on which no information is found in the papers.

4. Any location up to 15 kilometers away from a spray path coordinate virtually any time--including years later--after spraying, is considered in the exposure zone, the scores diminishing with increasing distance from the spray path. The highest exposure score appears to be given for being within 5 kilometers of spraying. The experimental data that exist from trials at Eglin Air Force Base, which, while not necessarily definitive, are the best available, suggest that virtually no Agent Orange would have travelled more than 2 kilometers from the spray line, and even at that distance, the amounts were minuscule. In CDC's analyses, nearly all troop locations that were "within 5 kilometers" of spraying were actually beyond 2 kilometers (i.e., between 2 and 5 kilometers), so even what is considered to represent the highest exposure in the American Legion study would likely have been almost no exposure at all in most instances. While it is entirely possible that some people were within 2 kilometers of spraying, particularly some time after spraying, they would likely be in the minority. The rationale for including distances up to 15 kilometers does not appear to be supportable given the set of facts available.

The investigators do not give examples of other successful occupational or environmental studies that have used less precise and accurate exposure measures than theirs, in support of their general claims quoted above. The herbicide and dioxin studies of which I am aware have had more stringent exposure criteria than did the American Legion study. Several studies have focused on occupational groups with known, direct exposure, including the studies of Swedish foresters, the current NIOSH studies of chemical production workers, and the Air Force Ranch Hand study. Studies of heavy environmental exposure in Missouri and Seveso include groups with known, direct exposure. In no case would a person living 15 kilometers from where herbicides were sprayed be assumed to have had significant exposure, unless some direct contact could be documented. A person living even 5 kilometers away from a plant

producing a dioxin-contaminated chemical would not be considered exposed comparably to workers in the plant, even if some dioxin were entering the general environment from the plant. While everyone acknowledges that conditions in Vietnam were different in many ways, there is no evidence suggesting that a scenario as unlikely as that underlying the American Legion exposure estimation method existed.

The comment that a "sizeable" number of men were classified as having had high exposure may be misleading. Although no description is given of the method used to divide the group into low, medium, and high exposure categories, it appears that divisions were made to create groups of convenient size for analysis. (This conclusion is based on examining the "Agent Orange Exposure Index" distribution in Figure 3 of the first paper.) It is clear that most of the 557 men classified as having had "high" exposure were very nearly the same as those classified as "medium," and that the entire range of scores, except for a few men in a long tail in the high end, was quite tight. Any array of individuals with specific numeric scores, which can vary by even small amounts, is divisible arbitrarily into groups, but doing so is not necessarily meaningful. To give an example, a man who was 10 kilometers from a spray would presumably have a higher score (for that occasion) than a man who was 15 kilometers, but in all likelihood, neither had a significant exposure, even if one is called "high" and the other "medium."

The authors claim a measure of validity for this index because they say that men could not have known, by the information they provided, how they would be classified. But according to data presented in the 1978 paper, men's self-reports of exposure were predictive of their exposure status as calculated. This could be due to the high correlation of the Agent Orange and combat indexes, suggesting that, in general, men who scored higher on the subjective combat exposure index also believed they had been more exposed to Agent Orange. Because of the gross imprecision represented by the Agent Orange index, the idea that it was actually measuring something else is a plausible explanation for the findings.

CDC's final exposure assessment method, used in their "validation study," was superior to the American Legion method. When CDC arrayed men by their exposure estimates, the range was quite small, with very few who had scores that would be considered high on an objective basis. This lack of clearly defined high exposure was borne out by the results of serum dioxin testing. In CDC's "validation study," the group of men who had served in heavily sprayed areas in Vietnam had dioxin levels no different from a similar group of men who had not served in Vietnam at all. If there were, in fact, large numbers of ground troops with high exposures, it is possible that CDC's method would have identified them accurately. The finding of only "background" dioxin levels in the ground troops contrasted sharply with significantly elevated levels in a group of Ranch Hands with known, direct exposure, providing assurance that a heavily exposed group is easily identifiable from one with low exposure, even 15 or 20 years after the exposure has ceased.

The American Legion study refers to testing for residual dioxin in the body as a means of detecting past exposure as "yet to be validated." It may be true that blood dioxin levels for individuals may not correlate directly with past exposure, but the method is relatively well validated for groups with high past exposure. CDC's validation study, a similar study conducted under the auspices of the New Jersey Agent Orange Commission, the recent Ranch Hand and NIOSH results, as well as studies of heavily exposed Missouri residents, and serum dioxin testing in individuals living in a dioxin-contaminated area near Seveso, Italy, all are consistent with heavy past exposure predicting persistently elevated blood dioxin levels. What remains unknown is the possible range of past exposure that could lead to current levels in the background range, and what the kinetics of elimination are in the background range. These gaps will be filled as the blood dioxin assay is applied more widely.

Ten-Year Mortality in the Seveso Population

A paper titled "Ten-year mortality study of the population involved in the Seveso incident in 1976," by P.A. Bertazzi and colleagues, appeared in the June 1989 issue of the American Journal of Epidemiology. The study reports on all deaths (almost complete ascertainment has been achieved) that occurred through 1986 in the population living in and around Seveso at the time of and subsequent to a 1976 chemical plant explosion, from which a dioxin-rich cloud settled over the area. For the purpose of health surveillance, the area in which the cloud settled was split into three sections, representing a small highly contaminated area (zone A), a somewhat larger, moderately contaminated area (zone B), and a larger area in which dioxin was still detectable above background levels (zone R). Long-term follow-up of cancer incidence and mortality have continued since the accident.

The paper reports that 27 of 556 individuals from zone A died in the 10 years after the accident; 170 of 3920 from zone B had died; and 1362 of 26,227 from zone R had died. Overall mortality rates and cause-specific rates were compared with corresponding rates for the entire Seveso region of Lombardy. The first five years and second five years of followup are analyzed separately, in addition to the analysis for the entire 10-year period. The abstract of the paper and the discussion claim a number of statistically significant findings, but an examination of the data themselves reveal these interpretations to be somewhat misleading. For example, a significant excess of deaths from cardiovascular disease is reported for the zone A population. Quoting from the paper:

The increase was particularly notable among males in the first quinquennium and among females in the second quinquennium. Males had a significant increase in chronic ischemic heart disease and cerebrovascular disease mortality.

There were two deaths from chronic ischemic heart disease among the males in zone A, both occurring between 1976 and 1981, giving a statistically significant excess over what was expected. No deaths from that cause were recorded during between 1982 and 1986, which is

JULY 1989

clearly less than expected, however, no notation of that appears in the table. Taken over the entire 10-year period, the two deaths do not represent a statistically significant elevation. The five deaths from cerebrovascular disease exceed the expected number for the entire 10-year period, but still constitute such a small number that no conclusion can be drawn from it alone. The zone B and R analyses for cerebrovascular disease show no excess whatsoever; in fact, there were fewer than expected such deaths among females in zone B and males in zone R.

Taking another example, the authors note a "clearly elevated brain cancer mortality among males, first period, and females, second period, in zone R," which they say raises "a hypothesis which warrants further investigation." In total, there were five brain cancer deaths among men and five among women for the entire 10-year period, and for the whole period, this was not significantly elevated, despite the fact that for men, more occurred during the first five years and for women, more during the second. This sort of variation in rates is well within statistical expectations, and should not be accorded particular relevance.

As one would expect from a study with relatively few deaths, a number of subanalyses show more deaths than expected, and a number show fewer than expected. Overall, however, no real differences in either mortality from all causes or mortality in larger categories (e.g., all cancers) is noted. The authors do caution about drawing conclusions from this study, with its inherent size limitations, and state that the results "do not permit conclusively associating any of the noted increased risks with the ICMESA accident." The way the results are presented, however, suggests that major excesses exist for certain causes of death in the Seveso population. An independent look at the data does not support that conclusion. It is, of course, important that surveillance of this possibly heavily exposed population continue, but the mortality data to date do not give cause for alarm.