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The Veterans Administration and other federal agencies are conducting studies of their effects on humans, with special focus on veterans of Vietnam, where "Agent Orange" was used.

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Few environmental or occupational health issues have received the sustained international attention that has been focused on the chlorinated dibenzo-*p*-dioxins—especially 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Much of the present concern centers on veterans of the Vietnam conflict, who may have been exposed to TCDD, a contaminant of the military defoliant Agent Orange. The public has become even more familiar with this dioxin because of improper disposal of toxic wastes in Missouri and New York; through reports of contaminated fish in the Great Lakes and Michigan; and as a consequence of publicity about a large PCB transformer fire in the State Office Building in Binghamton, N.Y. However, what drives the controversy is the veterans issue and the potentially larger question of whether human health has been significantly affected by the widespread use of dioxin-contaminated herbicides to enhance agricultural production.

Agent Orange in Vietnam

The use of herbicides to control vegetation has been one of the most persistent controversies arising from the Vietnam War. The U.S. Air Force applied most of these herbicides to dense jungle areas to uncover hidden enemy staging areas, to clear vegetation from the vicinity of military bases and along lines of communication, and to destroy the enemy's crops. The objectives were to provide defoliated zones, so that the number of ambushes would be reduced and enemy attacks could be disrupted. The most commonly used defoliant was Agent Orange, a mixture of the normal butyl esters of the two commercial herbicides, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). For many years, these materials had been employed for brush control in forests and rangelands and for weed control in agriculture throughout the U.S.

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During the five-year period from 1965 to 1970, the U.S. Air Force applied more than 40 million L of Agent Orange in South Vietnam. About two million American military personnel served one-year tours during the same period. Recently, many veterans of that era have reported medical problems that might stem from exposure to Agent Orange during their military assignments. Their complaints have ranged from tingling sensations in the extremities to rare forms of cancer. Some veterans have fathered children with birth defects and have suggested that Agent Orange is the culprit. Nevertheless, the basis for resolving the Agent Orange controversy must, in large measure, stem from the results of scientific inquiry.

Accordingly, the Veterans Administration (VA), in cooperation with other federal agencies, has begun extensive health studies of veterans exposed to Agent Orange and its dioxin contaminant 2,3,7,8-TCDD during the Vietnam conflict. In addition, numerous studies of nonveteran populations exposed to the phenoxy herbicides and TCDD have been encouraged and funded by several agencies of the federal government.

Problems with human studies

To conduct epidemiologic studies of human populations exposed to the phenoxy herbicides and their dioxin contaminants, it is first necessary to know what health outcomes should be selected for study. Second, one must be able to identify a study cohort with a high likelihood of exposure and a control group with a low or zero probability of exposure. Finally, a sufficient number of individuals in each cohort must be located, recruited, and examined to impart statistical validity to the results.

These three requirements, so important for the conduct of valid studies, are in themselves not clearly defined with respect to either the chemicals used in Vietnam or the population at risk. Health studies of the effects of phenoxy herbicides are difficult enough under conditions of normal agricultural use, but they become much more complex when conducted with cohorts briefly exposed more than a decade ago under conditions of war in a tropical environment.

The problems inherent in conducting epidemiological studies of Vietnam veterans are similar to those encountered in conducting studies of individuals and families who live, or have lived, near dioxin-contaminated toxic waste dumps. Heath, for example, wrestled with problems of carrying out field epidemiological studies on the residents of Love Canal (Niagara Falls, N.Y.) (*1*).

Phenoxy herbicide toxicity

TCDD toxicity in animals. Acute toxic effects induced by TCDD vary markedly among different species. For example, as little as 0.6–2.0 μg of TCDD/kg of body weight given orally to guinea pigs killed half of the male animals (*2*). However, in the hamster, TCDD is much less toxic, with an oral LD_{50} of 1157–5051 μg/kg of body weight (*3*, *4*).

TCDD is teratogenic in mice and causes an increased frequency of cleft palate as well as kidney abnormalities (*4*). In rats, TCDD does not produce a teratogenic effect, but does show embryo- and fetotoxicity (*5*). Also, it is carcinogenic in rats and mice after long-term ingestion at levels that induce toxic effects (*6*, *7*).

Toxicity in humans. Precise information concerning adverse effects of 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD is lacking. Acute and subchronic effects are reported quite uniformly following accidental and industrial exposures and suicide attempts, but there remains considerable scientific debate about the nature of delayed and long-term effects. Much of the medical knowledge of the effects of 2,4-D and 2,4,5-T exposure of humans is derived from case histories. Since many of the individuals described in such reports were exposed to multiple chemical agents, it is difficult to determine which chemical(s) produced the specific symptoms or health problems. Of the vast array of symptoms attributed to 2,4-D, the most consistently reported complaints involve behavioral, nervous system, liver, and intestinal problems.

Medical data associated with exposure to 2,4-D come primarily from spraying incidents, while data for 2,4,5-T and TCDD come from industrial exposures. Since the beginning of commercial production of 2,4,5-T, numerous industrial incidents have involved exposure to trichlorophenol, 2,4,5-T, and TCDD. Fifteen of the 23 episodes recorded in the literature apparently resulted from occupational exposures during industrial production of chlorinated phenols. However, on eight occasions, personnel were exposed either during cleanup operations or by working in improperly decontaminated workshops (*8*). The effects of 2,4,5-T could not be clearly distinguished from the possible effects of TCDD. Symptoms attributed to

The military use of herbicides in South Vietnam

The first shipment of Herbicides Purple and Blue was received at Tân Sơn Nhứt Air Base, Republic of Vietnam, on Jan. 9, 1962. These were the first military herbicides used in Operation RANCH HAND, the tactical military project for the aerial spraying of herbicides in South Vietnam. Two additional phenoxy herbicide formulations were received in limited quantities in South Vietnam and evaluated during the first two years of Operation RANCH HAND. These were code-named Orange and White, and had been evaluated and subsequently brought into the spray program. The use of Herbicide Orange replaced all uses of Purple, Pink, and Green, and it eventually became the most widely used military herbicide in South Vietnam. The composition and quantities of the herbicides used in South Vietnam are shown below.

Number of liters of military herbicide procured by the U.S. Department of Defense and sprayed in South Vietnam from January 1962 to October 1971

Code name	Herbicide	Liters	Period of use
Orange	2,4-D: 2,4,5-T	40 299 005	1965–70[a]
White	2,4-D: picloram	21 322 790	1965–71[b]
Blue	Cacodylic acid	4 353 005	1962–71[b]
Purple	2,4-D: 2,4,5-T	548 833	1962–65
Pink	2,4,5-T	464 820	1962–65
Green	2,4,5-T	31 070	1962–65

[a] Last fixed-wing mission of Orange, April 16, 1970; last helicopter mission of Orange, June 6, 1970.
[b] Last fixed-wing mission, Jan. 9, 1971; all herbicides under U.S. control stopped Oct. 31, 1971.

Estimated quantities of herbicides and TCDD disseminated in South Vietnam from January 1962 to February 1971

Chemical	(kg)
2,4-D[a]	25 374 450
2,4,5-T[a]	20 063 910
TCDD[b]	167
Picloram	1 379 760
Cacodylic acid	1 609 695
Total herbicides	48 427 982

[a] Expressed as the acid equivalents.
[b] The mean TCDD concentration in Herbicide Purple was estimated at 32.8 ppm. The mean TCDD concentration in Herbicides Pink and Green was estimated at 65.6 ppm. The mean TCDD concentration in Herbicide Orange was estimated at 1.98 ppm.
Source: Young, A. L. et al. "The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and Its Associated Dioxin," Technical Report OEHL-TR-78-92; USAF Occupational and Environmental Health Laboratory, Brooks AFB, Tex. 78235; 1978. Available from National Technical Information Service, document AD-A062-143.

2,4,5-T and TCDD exposure include all of the symptoms of 2,4-D exposure, plus a skin disease, chloracne.

Many scientists believe that chloracne is the "hallmark" of exposure to dibenzo-*p*-dioxins, especially 2,3,7,8-TCDD (*9*). Chloracne is a skin reaction characterized by an acniform dermatitis with comedones (blackheads) and inclusion cysts or papules and frequently pustules so severe that they cause permanent scarring. Morphologically, it is similar to adolescent acne, but it is usually more severe, particularly on the upper face, ears, and neck. Active chloracne lesions have been reported many years after exposure to TCDD, but the condition usually clears up spontaneously in a few months. Premature aging of involved skin areas has been reported in some instances, as well as the appearance of hyperpigmentation (*10*).

Mortality experience

Recently, a number of epidemiological studies have reported on mortality experiences in industrial settings. In January 1980, Zack and Suskind (*12*) published the results of a 30-year follow-up study of 121 chemical workers who had developed chloracne following exposure to TCDD in an industrial accident at Nitro, W.Va. The plant involved the manufacture of trichlorophenol. Although they observed no apparent excess in total mortality from cancer or cardiovascular disease, they could not consider the results conclusive because of the small cohort and the relatively small number of deaths observed.

In a 1983 report, Zack and Gaffey (*13*) expanded this study to include 884 men, of whom 721 were still alive and 163 had died. Analyses of these data showed no excess in total deaths or in deaths caused by cancer or other diseases of the nervous, circulatory, respiratory, or digestive systems. Although most of the men in this larger population were employed in the trichlorophenol plant, and thus were potentially exposed to TCDD, they did not develop chloracne.

In August 1980, Ott et al. (*14*) examined the mortality experience of 204 persons employed by Dow Chemical Company who were exposed to 2,4,5-T during its manufacture from 1950 to 1971. Among the 11 deaths observed, (20.3 expected), one was caused by a respiratory malignancy (3.6 malignant neoplasms expected). Thus, within the scope of this mortality survey, no adverse effects were observed with respect to occupational exposure to 2,4,5-T or its feedstock, 2,4,5-trichlorophenol.

In a subsequent report, Cook et al. (*15*) detailed a study of 61 males involved in a chloracne incident at Midland, Mich., in 1964. Of these men, 49 developed chloracne while working in a trichlorophenol manufacturing plant operated by Dow Chemical Company. Within the limits imposed by the size of the cohort and the length of the follow-up, TCDD apparently had no adverse effect on mortality experience, and deaths from cardiovascular disease or cancer were statistically insignificant.

Soft-tissue sarcoma

Soft-tissue sarcomas (STS) are a complex and diverse group of malignant neoplasms that usually originate in muscle, fat, and fibrous connective tissue, such as tendons or ligaments; they are found less frequently in blood vessels and nerves that serve these tissues. They account for about 1% of all malignant neoplasms and about 2% of all cancer deaths. The average annual age-adjusted incidence rate is 3.89/100 000; it is estimated that 8000 new STS cases are diagnosed in the U.S. each year (*16*). The most common histologic types are malignant fibrous histiocytoma, leimyosarcoma, sarcoma not otherwise specified, lipo-

sarcoma, and fibrosarcoma, in that order (*17*). Little is known about the etiology of STS. The epidemiologic study of STS has been especially difficult because of uncertainties in the morphologic classification of this diverse group of neoplasms. In addition, the International Classification of Disease (ICD), which is anatomic site-oriented, fails to categorize these neoplasms as to cell type and other morphologic characteristics.

The possibility that occupational exposure to phenoxy herbicides and chlorophenols may induce rare forms of cancer in humans, such as STS, has been suggested from recent case control studies in Sweden. The Swedish studies have shown that persons reporting exposure to the chemicals have a five- to sixfold higher risk of developing STS, compared to unexposed persons (*18*, *19*). In consideration of possible recall bias among cancer patients regarding their past exposure to certain chemicals, a subsequent study included controls consisting of colon cancer patients. This latter study still indicated a fivefold increase in the risk of developing STS among persons reporting exposure to the herbicides (*20*).

Other studies of workers, however, have not yet replicated these significant observations. In a recent Finnish study of a cohort of 1926 men who had sprayed phenoxy herbicides from 1955 to 1971, no cases of death from STS or lymphomas were reported (*21*). But as the authors indicated, these results should be interpreted with caution because of study limitations, such as the small size of the cohort, a short follow-up period, and brief and low exposure to herbicides or TCDD.

Similarly, a case control study of STS by New Zealand investigators failed to show higher risk in the occupational groups involving agriculture and forestry (*22*). Phenoxy herbicides have been used extensively in New Zealand in both industries. Since the occupation at the time of diagnosis might not have contributed directly to the development of STS, further investigations into the individuals' exposures to the herbicides are warranted. Indeed, even the Swedish investigators stated that if "agriculture" and "forestry" are taken as a crude measure of exposure to the herbicides, no significant increase in the risk of STS or malignant lymphoma was found (*23*).

Several cases of STS have been reported among American workers involved in the manufacture of herbicides (*24–26*). These industrial workers, in contrast to those who apply herbicides, are believed to be exposed to relatively high levels of TCDD. On the other hand, no STS cases have been reported in studies of workers involved in the manufacture of herbicides in either West Germany (*27*) or Czechoslovakia (*28*).

Defoliation. *This area in Vietnam was sprayed with Agent Orange.*

Except for mesothelioma, which is known to result from asbestos exposure, and angiosarcoma of the liver, which is known to be caused by vinyl chloride, no cancers of this type have an etiology related to chemical exposure. A small fraction of STS may be induced by heavy external radiation therapy for various benign disorders or malignant tumors (*29*).

Birth defects

Outside the U.S. The first reports of human birth defects attributed to Agent Orange appeared in Vietnamese newspapers in June 1969. As a result of expressions of public and scientific concern arising from these reports, Cutting et al. (*30*) and Meselson et al. (*31*) conducted two independent surveys of South Vietnamese hospital records. Although neither report reached definite conclusions on the validity of the accusations, both reports acknowledged that searches of the records probably would have revealed any marked increase in birth defects or introduction of a striking defect, such as the defects produced by thalidomide. Subsequent reports by Tung et al. (*32*) in 1971 and Rose and Rose (*33*) in 1972 centered on clinical observations and interviews conducted in Hanoi with refugees who claimed that they were repeatedly sprayed with defoliants in South Vietnam. The authors reported unusually high rates of abortions and severe birth defects in both humans and domestic animals.

Perhaps the most thorough assessment of South Vietnamese birth records was conducted at the request of the National Academy of Science by Kunstadter (*34*) between April 1972 and January 1975. Kunstadter's research relied on U.S. Department of Defense records of geographic and temporal distribution of herbicides. It was also based on the unpublished and published statistical reports of births in Tu Du and Húng Vuong hospital maternity facilities in Saigon and detailed examination of patient records. Interviews with patients' mothers at the Barsky Unit, Cho Rây Hospital, Saigon, which drew patients from all over the country for surgical repair of birth defects and other injuries, were also included in his evaluation.

Records of birth defects and perinatal mortality from the hospitals showed few consistent statistically significant results to support the hypothesis that there was a positive association between the military use of herbicides in Vietnam and the incidence of birth defects in children born to mothers exposed during pregnancy. Cleft lip increased as a proportion of all malformations during the period of heavy spraying. However, this increase continued after spraying had stopped, suggesting a trend unrelated to herbicide exposure. An increase in the stillbirth rate following the close of the

heavy spraying period was also inconsistent with the hypothesis, unless the teratogenic effects were persistent and cumulative.

Analysis of the records of Barsky Unit patients suggested that, with regard to the distribution of patients by diagnosis and sex over time and by geographic region, there was no consistent, statistically significant support for the hypothesis. Within the analysis of distribution of diagnoses and known risk factors, only the tabulation of variations in proportion of cleft lip patients with *relatives* who also have cleft lip was statistically significant. In that case, one might infer that if there was an association between herbicides and cleft lip, there was a positive interaction between herbicides and *other causes* of cleft lip.

Donovan et al. (*35*) recently completed a case control study of the effect of Vietnam service on the development of congenital anomalies. This Australian birth defects study examined records from 34 hospitals and four cytogenetic laboratories to identify infants born with birth defects. Matched healthy infants born in the same hospitals served as controls. The fathers of 8517 cases and an equal number of controls were identified, and the nature of their total service in the army was determined, as well as that of their duty in Vietnam. In all, 127 of the fathers of children with birth defects were Vietnam veterans, while 123 of the fathers of normal, healthy, children were Vietnam veterans. There was no evidence that service in Vietnam increased the risk of fathering a child with a birth defect.

In New Zealand, a number of workers have been exposed to phenoxy herbicides during their manufacture and spraying. Both sprayers and their wives are exposed during the handling and field spraying of chemicals. Smith et al. (*36*), in a recent survey of professional sprayers and a control group of exposed agricultural contractors, determined the number of births among the families of 989 study participants. The sprayers exposed to 2,4,5-T had a 1.19 times greater likelihood of fathering children with birth defects. The wives on the other hand had a lesser risk of having miscarriages, by a factor of 0.89. The differences are not statistically significant. Exposure of the wives also had no other detectable reproductive effect.

In the U.S. The U.S. EPA, the U.S. Department of Agriculture (USDA), and the National Institute for Occupational Safety and Health (NIOSH) have all completed limited studies on the potential associations of phenoxy herbicides with human spontaneous abortions and birth defects.

There was no evidence that service in Vietnam increased the risk of fathering a child with a birth defect.

Two studies were conducted by EPA to evaluate the relationship between herbicide spraying and reproductive errors. In 1979, Johnson (*37*) released the data used by the agency in the decision to order the suspension of registrations of 2,4,5-T for uses in forest, rights-of-way, and pastures. He reported that the incidence of spontaneous abortions over a six-year period in Alsea, Ore., was found to be higher than the rates in two other regions of Oregon that had lower rates of 2,4,5-T usage. Although a cyclic pattern in the incidence of spontaneous abortions in the Alsea group correlated positively with the pattern of annual 2,4,5-T spray usage, Johnson acknowledged that EPA did not consider this as proof of a cause-and-effect relationship.

One of the major uses of 2,4,5-T is for weed control in rice fields. In another study sponsored by EPA, the incidence of cleft palate over a period of 32 years in Arkansas was shown not to be related to the usage of 2,4,5-T. The incidence of cleft palate for both of the regions with a low proportion of rice acreage (indicating low exposure to 2,4,5-T) and for regions with high production of rice (indicating high 2,4,5-T exposure) increased over the years studied. This trend was attributed to better detection of cleft palate, and not to herbicide usage (*38*).

The USDA sponsored a study designed to evaluate the relationship between exposure of human males to 2,4-D and the incidence of spontaneous abortions in their wives. In this study reported by Carmelli et al. (*39*), questionnaires pertaining to these two factors were mailed to almost 15 000 people who were employed in occupations involving the manufacture or use of herbicides. From the respondents, a group of 134 cases of miscarriages was selected and compared to a control group of 311 cases of live births. The cases were analyzed to determine the incidence of parental exposure to 2,4-D prior to conception and the presence of other relevant confounding factors, such as smoking, illnesses, and drug use. The data were obtained or verified by telephone interviews.

No positive association was established between 2,4-D exposure and abortions for the entire study population. For a group of 21 cases of wives of young forestry and commercial workers, an association was suggested, but was not found for any other subgroup. Further investigations were suggested, in order to clarify whether this relationship resulted from biases in study design or reflected a real increase among this small subset.

In November 1979, NIOSH received a request to determine whether an excess number of birth defects occurred among the children of maintenance employees working for the Long Island Railroad, N.Y., and whether these defects may have been caused by exposure to 2,4,5-T. Honchar (*40*) investigated 170 live births observed from among the study population of approximately 1400 employees. It was found that all major birth defects combined, as well as inguinal hernia, were underrepresented in the study population: 3 observed vs. 3.81 expected for major birth defects; 2 observed vs. 2.3 expected for inguinal hernia. However, minor defects such as the congenital foot deformity *metatarsus adductus* (8 observed vs. 3.47 expected) and tear duct obstruction (2 observed vs. 0.22 expected) were both significantly overrepresented in the study population. Honchar concluded that these minor defects were probably overrepresented in the study population because of diagnostic bias.

In summary, it would appear that

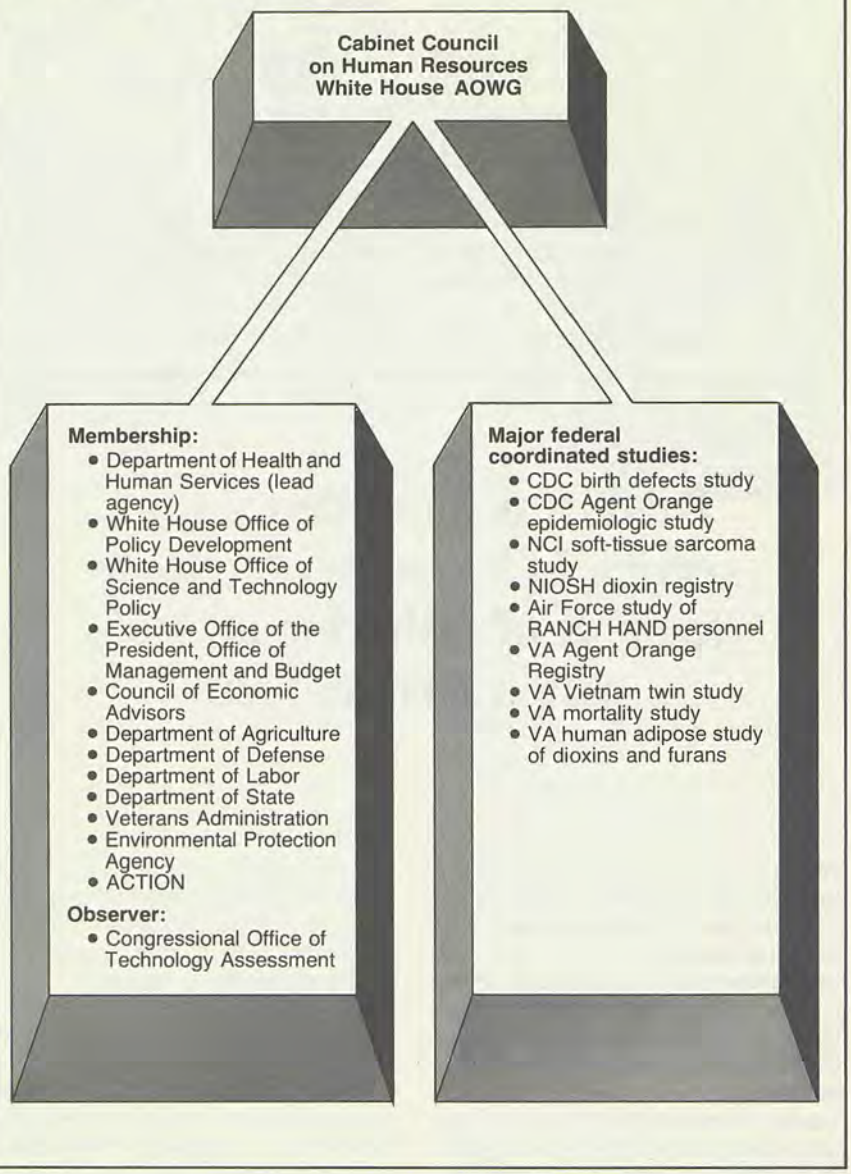
based on the studies to date, there is very little epidemiologic data associating TCDD or the phenoxy herbicides with any long-term health effects in humans other than chloracne. Conversely, as noted by Wolfe (*41*), neither is there strong evidence to validate the absence of such effects. Most studies have not included sufficient numbers of subjects to detect an increased risk of an uncommon condition. Also, the period of observation in many studies has been inadequate to detect an illness with a long latency period between exposure and illness.

Health status of Vietnam veterans

As of May 1983, more than 17 000 Vietnam veterans had submitted claims to the VA for disabilities that they believe are the result of exposure to herbicides. These claims describe more than 130 different effects in five major categories: psychiatric, dermatological, reproductive, neurologic, and carcinogenic. The scientific data validate specific links between exposure to Agent Orange and TCDD in the sense that some symptoms reported by the veterans have also been documented in other cases of exposure to the herbicides or to TCDD. But most of these symptoms, such as peripheral neuropathy, fatigue, weight loss, and some psychological disturbances, are acute symptoms that manifest themselves shortly after exposure. Such symptoms arising years after the last known exposure are most likely not caused by 2,4-D and 2,4,5-T or TCDD. A large number of veterans have claimed dermatological problems, and many believed they had chloracne. To date, however, only a few cases of chloracne have been confirmed by physical examination in this group of veterans.

Despite the lack of solid scientific evidence to support the veterans' allegations that Agent Orange and its dioxin contaminant are the cause of their difficulties, one recognizes that some of the veterans have experienced serious health problems. Therefore, the purpose of many of the government studies is to determine whether Agent Orange is responsible for these health problems. If Agent Orange is not the causative agent, other factors associated with the Vietnam War may be responsible. Consequently, the goals of other research efforts are to determine whether Vietnam veterans as a group are experiencing more or different health problems than their counterparts who did not serve in that part of the world. In such a complex situation, no single study can provide all of the answers. Thus, there is a need for a number of different approaches to examining the health of the Vietnam veteran.

FIGURE 1
The White House Agent Orange Working Group (AOWG) and several studies it coordinated



Current federal investigations

What has been the response of the federal government to the critical issues raised by Agent Orange and dioxin exposure? In 1981, the President established the White House Agent Orange Working Group (AOWG) of the Cabinet Council on Human Resources. While AOWG does not conduct any research, it is charged with being the overall coordinator, clearinghouse, and evaluator of the federal research effort. Under the umbrella of AOWG, all of the federal agencies involved in research and policy related to Agent Orange and other herbicides used in Vietnam are drawn together and work together. Conclusions reached by federal projects are provided to the Secretary of the Department of Health and Human Services so that the administration and Congress can develop policy based on scientifically supportable facts. Figure 1 shows the structure and membership of AOWG and some of the major research projects currently being coordinated and monitored.

The VA initiated its involvement with Agent Orange through the development of a communication process for gathering scientific and medical information. In early 1978, it established the Agent Orange Registry in order to accomplish four objectives:

• to identify all Vietnam veterans expressing a concern about the possible adverse health effects of their exposure to Agent Orange;

• to provide a mechanism for Vietnam veterans to voice their concerns to a physician, receive a physical examination, and obtain responsible answers to some of their questions;

• to serve as a mechanism for follow-up of these veterans if, at a later date, new information develops as a result of the various research efforts under way or being planned; and

• to obtain, as a by-product, some preliminary information on the current health status of the veterans who have participated in the registry.

The Agent Orange Registry provides a listing of names and addresses, together with some background data on a self-reported group of veterans with service in Vietnam. A complete physical examination and a group of baseline laboratory tests are provided to each veteran. The information from this effort is currently being computerized. The agency is in the process of collating the data to determine whether or not there are any significant health trends in these individuals that might suggest areas for further investigation. Although we have collected information on a large number of veterans, great caution must be exercised to analyze and interpret the data properly because of the self-selection of the sample, lack of precision in the reporting of exposure, and possible selective recall of symptoms and exposure.

With these limitations in mind, we have attempted to compare distribution of malignant neoplasm cases in the Agent Orange Registry with that in a reference population. These data are presented in Table 1. Subjects in the SEER (Surveillance Epidemiology End Results) program were selected for the reference population. The Biometry Branch of the National Cancer Institute collected data on cancer incidence and mortality in the U.S. for a five-year period (1973–1977) through 11 SEER program centers. The total number of subjects in the SEER program represents about 10% of the U.S. population and is fairly representative with respect to age.

Data on a total of 84 456 veterans were computerized in the Agent Orange Registry as of May 17, 1982. Among these veterans, 720 were diagnosed as having malignant neoplasms (ICD 140-208); 263 had previous personal histories of malignant neoplasms (ICD V 10.0-V 10.9); 2 had in situ carcinoma of the skin; and 18 had neoplasms of uncertain behavior or nonspecific nature (ICD 236-239). To be comparable with the SEER data, 136 cases of nonmelanoma cancer of the skin (ICD 173) reported in the Agent Orange Registry were excluded from the analysis.

Although nonmelanoma cancer of the skin is the most common malignant neoplasm in the white population of the U.S., statistics on skin cancer are usually incomplete, because most skin cancer patients are seen and treated in physicians' offices and are not hospitalized. The primary source of data for cancer registries including the SEER program is the hospital patient file.

The distribution of malignant neoplasm cases in the SEER program was calculated using the number of malignant cases diagnosed from 1973 to 1977 among U.S. males aged 25–39. This age group should include most of the Vietnam era veterans and, therefore, would serve as a reasonable comparison group. In general, no significant disparity in the proportion of cancer of various sites was noted between the two groups. Proportions of STS and skin cancer in the registry were not different from the SEER population: 1.9% vs. 2.6%; 9.1% vs. 11.7%. Some differences, however, were found for cancer of the buccal cavity and pharynx, and lymphomas.

The 95% confidence limits for differences in proportions for these two sites were 1.2–5.7% and 1.6–8.4%, respectively. In other words, proportions for these sites in the registry were higher than expected from the reference population. Whether these marginal but statistical differences are artifacts or something of importance is not clear at this time. A recent study by Hardell et al. (*42*) also implicated an association of phenoxy acid or chlorophenol exposure with nasal and nasopharyngeal cancer. We will continue to monitor the registry data.

The VA in cooperation with EPA agreed to study levels of 2,3,7,8-TCDD in adipose tissue from a select group of U.S. males.

Assay of human adipose tissue

Since TCDD is known to accumulate preferentially in the adipose tissue of certain species of laboratory animals, it was suggested early in the history of the Agent Orange issue that the analysis of human fat for TCDD might provide a way to determine earlier Agent Orange exposure. A relation between the presence of this substance and health problems had also been suggested (*43*). Although methods for TCDD analysis had improved in recent years, no such study was carried out in humans with known exposure to herbicides containing this toxic contaminant. Consequently the VA embarked on a small feasibility study to test the methodology and to determine whether conclusions might be drawn regarding the significance of the results. The study was carried out with three groups of adult males:

• twenty Vietnam veterans, all but one of whom claimed health problems related to Agent Orange exposure, who volunteered for the fat biopsy;

• three U.S. Air Force officers with known heavy and relatively recent exposure in connection with herbicide disposal operations, including one who served in Vietnam; and

• ten veterans with no service in Vietnam and no known exposure to herbicides who were undergoing elective abdominal surgery and volunteered to serve as controls.

The procedure called for the removal of 10–30 g of subcutaneous adipose tissue from the abdominal wall. This was accomplished surgically under local anesthesia. Precautions were taken before, during, and after the procedure to avoid contamination by compounds such as hexachlorophene that could contain TCDD. Specimens were collected in glass containers previously rinsed with acetone and dried before use. All tissues

TABLE 1

Number and percent distribution of malignant neoplasm cases [a]

Primary site (ICD)	Number of cases	Percent distribution	
		Registry	SEER [b]
Buccal cavity and pharynx (140–149)	46	7.9 [c]	4.5
Digestive system (150–159)	68	11.6	12.2
Respiratory system (160–169)	60	10.3	8.5
Bones and joints (170)	8	1.4	1.1
Soft tissue (171)	11	1.9	2.6
Skin (172) [d]	53	9.1	11.7
Breast (174, 175)	3	0.5	0.06
Male genital system (185, 186, 187)	80	13.7	16.0
Urinary system (188, 189)	32	5.5	6.1
Eye (190)	4	0.7	0.5
Brain and other nervous system (191, 192)	28	4.8	6.0
Endocrine system (193, 194)	20	3.4	6.5
Lymphomas (200, 201, 202)	117	20.0 [c]	15.0
Multiple myeloma (203)	7	1.2	0.4
Leukemia (204–208)	30	5.1	6.0
Others and ill-defined sites (195–199)	17	2.9	3.0
Total	584	100	100

[a] Among 84 456 veterans recorded in the Agent Orange Registry and compared with a reference population.

[b] SEER (Surveillance Epidemiology End Results): percent distribution of malignant neoplasm cases diagnosed from 1973 to 1977 by primary site, males age 25–39, all races and all areas excluding Puerto Rico.

[c] The 95% confidence limits for differences in proportions do not include zero.

[d] Excluding basal and squamous cell carcinomas.

were refrigerated during shipment to the assay laboratory. Each of the volunteers had a medical history, physical examination, and routine clinical chemistry. The details of military service in Vietnam from the volunteer's report and his service record were examined to evaluate his potential exposure to herbicides using the dates, location, and nature of his service. From these a rough estimate of the likelihood of exposure to TCDD was made without knowledge of the assay results.

The extraction and assay of all samples for TCDD were conducted at the University of Nebraska, Midwest Center for Mass Spectrometry, Lincoln, Neb. Gas chromatography/high resolution mass spectrometry was employed for quantification of 2,3,7,8-TCDD and coeluting isomers. Extracts that contained materials giving signals greater than 2.5 times noise at the exact mass of TCDD (that is, m/z 321.8936 ± 0.0020) over the integration period were reanalyzed. For the second analysis, signal profiles of m/z 321.8936 and m/z 319.8965 were monitored over the elution period of 2,3,7,8-TCDD (determined by injection of standard solutions). A positive detection was reported if signals were observed above the detection limit and if their intensity ratio was consistent with the presence of four chlorine atoms in the molecule. Samples meeting all criteria except the isotope intensity ratio were considered to contain "not detectable" levels of TCDD. For these samples, it was judged that the presence of TCDD is not disproved by the observation of an incorrect isotope ratio at these low concentrations; rather, the presence of TCDD is not confirmed.

The analysis revealed that of the 20 veterans who served in Vietnam, seven had no detectable TCDD with the limit of detection at 2–6 parts per trillion (ppt). Another two had detectable material that could not be validated as TCDD, and the results for one were considered equivocal because the measured value was only questionably above the detection limit. Five of the 10 remaining Vietnam veterans had TCDD in amounts from 5 to 7 ppt. Three Vietnam veterans had TCDD in amounts from 9 to 13 ppt; one had 63 and 99 ppt; and another had 23 and 35 ppt.

Of the 10 control (unexposed) veterans, four had TCDD identified in their fat (6, 7, 7, and 14 ppt). Two other veterans had values low enough to be considered equivocal, and in three instances, the detected material was not validated as TCDD. The remaining veteran had no detectable TCDD.

One of the three Air Force officers with known heaviest exposure had no identified TCDD in his fat. The unidentified substance in his case and the TCDD measured in the other two officers was never more than 3 ppt above the limit of detection.

Among the 20 Vietnam veterans there was no uniformity of symptoms, either immediately after exposure, at the time of biopsy, or during the intervening period. No one symptom or group of symptoms was common to veterans with detectable TCDD in their fat. The presence of TCDD did not mean ill health, nor did its absence indicate good health. No detailed statistical analysis of this small pilot series was attempted.

In summary, the results of this very complex and technically difficult analysis indicated that very low levels of TCDD, believed to be 2,3,7,8-TCDD, could be detected in human adipose tissue in the range 3–99 ppt. The levels, however, did not correlate well with known exposure and nonexposure, and there was no correlation with health status. The study results, however, did indicate that the assay method was feasible, but would serve no clinically or administratively useful purpose until additional data were available on background levels of TCDD in the general U.S. population. Accordingly, the VA in cooperation with EPA, agreed to study levels of 2,3,7,8-TCDD in adipose tissue from a selected group of U.S. males.

EPA has been collecting adipose tissue from the U.S. general population by region, age, sex, and race. This National Adipose Tissue Bank was started in 1968 and now contains specimens from over 12 000 individuals. Adipose tissue from approximately 550 males born between 1937 and 1952 is available from this bank. Many of these men served in the military during the Vietnam era, and some served in Vietnam during the period of Agent Orange use. A retrospective

study of their adipose tissue may establish data on background levels of 2,3,7,8-TCDD in the U.S. male population, as well as whether service in the military and especially in Vietnam has had an effect on the levels of TCDD in adipose tissue.

The study will be conducted in three phases. Phase I will obtain the name and social security number for the approximately 550 males noted above. This information will be used to determine military service status. Phase II will be the development of analytic methods for the determination of selected dioxins (especially 2,3,7,8-TCDD) and furans in human adipose tissue. The method will be subjected to rigorous interlaboratory validation by an independent analytic referee, such as the Association of Official Analytical Chemists. Phase III will be the analysis of the adipose tissue and the preparation of a final report. Phases I and II should be completed within calendar year 1983, and the report from Phase III should be available in early 1985.

Vietnam veteran mortality study

The VA initiated a large mortality study that will compare cause-of-death profiles between veterans with service in Vietnam and comparable veterans with no service in Vietnam. Because there are no estimates of the population at risk, the study will provide only proportionate mortality ratio (PMR) data. The study will use existing records to identify a group of approximately 60 000 deceased veterans and determine cause of death and Vietnam service status. The study will also include independent validation of the computer data base used to identify deaths.

It is important to note that the mortality study will not provide information specifically related to a reason for greater or lesser relative frequency or specific cause of death. Nonetheless, the study will provide a large amount of potentially useful information on Vietnam veteran mortality. In addition, it will provide ideas for future research. The results are to be reported in late 1984.

Vietnam Experience Twin Study

The Vietnam Experience Twin Study was begun by a group of research staff members at the VA Medical Center, St. Louis, Mo. The study will identify pairs of identical twin veterans of which one twin served in Vietnam during the period of Agent Orange spraying and the other served in an area other than Southeast Asia. Approximately 600 pairs of twins will be examined using a series of psychologic, physiologic, and biochemical tests.

The development of a protocol for the study and the establishment of a Twin Registry from which to solicit participants is now under way. The study will focus primarily on the total Vietnam experience rather than any single factor such as Agent Orange. If a sufficient number of identical twin pairs are identified, there may be an opportunity to draw some conclusions regarding the effects of specific aspects of the Vietnam experience such as combat, herbicide exposure, or use of insecticides. Following formal review of the protocol, the study is to begin in January 1984. A report on the results is planned for early 1986.

Birth defects

In 1981, the Centers for Disease Control (CDC) in Atlanta, Ga., began a study designed to determine if veterans are at an increased risk of having children with birth defects. Since 1968, CDC has maintained a registry of all babies born with defects in the greater metropolitan Atlanta area. Of the more than 15 000 children in this registry, approximately 7500 had significant anatomical defects at birth. The investigators will locate and interview both parents of approximately 5400 of the children in this group. In addition, the parents of 3000 matched control normal babies born during the same time period will be interviewed.

Since the major objective of this study will be to determine whether an unusually high proportion of fathers of babies born with defects served in Vietnam, information will be gathered about Vietnam service, as well as other factors that may be associated with occurrence of birth defects. If results demonstrate that a Vietnam veteran has an increased risk of fathering a child with a defect, it may be desirable to attempt to determine if the increase is associated with Agent Orange exposure or with some other factor(s). The study is scheduled to be completed by the end of 1983.

The Air Force health study

In 1979, the Air Force established the protocol for a comprehensive epidemiologic study of RANCH HAND personnel, a group of approximately 1260 men who conducted the fixed-wing aerial herbicide spraying missions in Vietnam from 1962 through 1971. The study is designed around the question, "Have there been, are there now, or will there be in the reasonably forseeable future, any adverse health effects among RANCH HAND personnel caused by repeated exposure to Herbicide Orange?"

The investigation is composed of three integrated elements—a mortality study of those individuals who have died since their exposure, a morbidity study to examine the current health status of the study subjects, and a follow-up study to look for delayed effects over the next 20 years. The mortality and morbidity study elements are being conducted simultaneously on RANCH HAND personnel and on a group of very carefully matched controls using personnel tracking procedures coupled with an extensive review of military medical personnel records; detailed face-to-face questionnaires to ascertain current and past health events as well as occupational and family data; and comprehensive physical examinations, psychological testing, and diagnostic laboratory studies to determine exact health status. Additional questionnaires and physical examinations are to be administered periodically during the follow-up phase.

In June 1983, a report was released comparing the mortality experience of

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1247 RANCH HAND personnel and 6171 comparison subjects (*43*). The comparison subjects were individuals assigned to selected Air Force units with the mission of flying cargo to, from, and in Vietnam during the same period. As of Dec. 31, 1982, 50 RANCH HAND and 250 comparison subjects had died. The mortality experience, including deaths caused by malignant neoplasms, of the RANCH HAND population was almost the same as that of the comparison group. No STS deaths were detected in either group. Although there was no indication that the RANCH HAND subjects suffered from any increased mortality or any unusual patterns of death, the study results should not be regarded as final because of the small sample consisting of young, healthy individuals and the relatively short follow-up period. The results of the initial questionnaire, current health status, and reproductive histories are to be released in late 1983.

Study of ground troops

Public Law 96-151 charged the VA to "design a protocol for and conduct an epidemiological study of persons, who while serving in the Armed Forces of the United States during the period of the Vietnam conflict, were exposed to any of the class of chemicals known as 'the dioxins' produced during the manufacture of the various phenoxy herbicides (including the herbicide known as 'Agent Orange') to determine if there may be long-term adverse health effects in such persons from such exposure." Efforts by CDC (through an interagency agreement with the VA) are under way to complete a protocol and to identify suitable cohorts. This will be a huge research effort that will include interviews and examinations involving several thousand veterans.

A major problem in the design of such a study is that there are very few records maintained that would link specific ground troops to herbicide exposure. Another problem encountered is that it is difficult to design data-collecting instruments and techniques when the health outcome variables are so ill-defined. However, much design work has been accomplished, and it is hoped that the study will begin early in 1984 and be completed by 1987.

Soft-tissue sarcoma studies

In view of concern raised by many veterans that their contact with phenoxy herbicides and TCDD during Vietnam service may increase the risk of developing STS, and because of the conflicting research findings in the scientific literature regarding association between exposure to phenoxy herbicides and STS, many epidemiological studies have been initiated in the U.S. to determine host and environmental risk factors for STS. The National Cancer Institute is conducting a case control study in the state of Kansas to evaluate the effects of occupational and environmental risk factors including herbicide exposure on the development of STS, non-Hodgkin's lymphoma, and Hodgkin's disease. A minimum of 100 white male cases of each cancer drawn from the University of Kansas Medical Center Cancer Data Service will be compared to controls matched to each case (3:1) by age, race, sex, and area of residence. Results of this study are due in mid-1984.

The VA, in collaboration with the Armed Forces Institute of Pathology (AFIP), has started a case control study of STS. A minimum of 500 STS cases selected from the AFIP registries will be compared to controls matched (2:1) to each case by age (±5 years), race, sex, and place of initial diagnosis. Phase I of the study will investigate whether military service in Vietnam increases the risk of developing STS. Phase II of the study will investigate other host and environmental risk factors for STS based on information obtained from interviews with subjects or their next of kin. Phase I of the study is scheduled for completion in the fall of 1984; Phase II will be completed in late 1985.

Since 1979, NIOSH has begun to develop a registry of U.S. workers involved in production of herbicides possibly contaminated with dioxin. As of May 1, 1983, about 4000 workers have been included in the registry. The enrollment of an expected number of 6000 workers will be completed by the end of 1983, and their mortality pattern, including deaths caused by STS, will be available in early 1985.

Unresolved controversies

Neither the government nor the scientific community has resolved the numerous environmental, medical, and political controversies involving the use of Agent Orange in Vietnam from 1962 to 1970 or the use of 2,4,5-T in U.S. agriculture. A report by the National Academy of Sciences in 1974 documented some of the environmental impacts of Agent Orange, but the arrangements that terminated the Vietnam conflict precluded additional scientific studies in that area. Such studies might have clarified current medical concerns about herbicide exposure. Moreover, to date, federal agency positions on environmental hazards associated with TCDD and 2,4,5-T are either not well defined or not uniformly accepted, thus perpetuating the controversy.

The scientific community must continue to conduct valid research on pertinent environmental and health-related issues to provide a reliable basis for appropriate decision making. The VA stands firmly committed to working closely with other agencies of the federal government, as well as with the private sector, to obtain as many answers as quickly as possible, consistent with sound scientific principles, to resolve this perplexing issue. The resolution of the controversy, however, will be achieved only following the public's acceptance of the outcome of scientific investigations. To that end, scientists must accept the responsibility for not only conducting quality research, but also for translating the results of their efforts for legislators, the courts, the media, and ultimately, the public at large.

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