Chapter 9: Reproductive Effects

Chapter 9 (continued)

Chapter 9 (continued)

Chapter 10: Neurobehavioral Effects

Chapter 10 (continued)

Chapter 11: Other Health Effects

Chapter 11 (continued)

Chapter 11 (continued)

Chapter 12: Research Recommendations

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INTRODUCTION

Between 1962 and 1971, U.S. military forces sprayed nearly 19 million gallons of herbicides over approximately 3.6 million acres in Vietnam. The preparation known as Agent Orange accounted for approximately 11.2 million gallons of the total amount sprayed. Herbicides were used to strip the thick jungle canopy that helped conceal opposition forces, to destroy crops that enemy forces might depend upon, and to clear tall grass and bushes from around the perimeters of U.S. base camps and outlying fire support bases. Most large-scale spraying operations were conducted using airplanes and helicopters, but considerable quantities of herbicides were sprayed from boats and ground vehicles, as well as by soldiers wearing back-mounted equipment. Spraying began in 1962 and increased greatly in 1967. After a scientific report in 1969 concluded that one of the primary chemicals used in Agent Orange, namely, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) could cause birth defects in laboratory animals, U.S. forces suspended use of this herbicide in 1970 and halted all herbicide spraying in Vietnam the next year.

As the decade wore on, concern about possible long-term health consequences of Agent Orange and other herbicides heightened, fueled in particular by reports from growing numbers of Vietnam veterans that they had developed cancer or fathered handicapped children, which they attributed to wartime exposure to the herbicides. Along with the concerns of Vietnam veterans, public awareness increased because of reports of health concerns surrounding occupational and environmental exposure to dioxin--more specifically, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), informally known as TCDD--a contaminant of 2,4,5-T. Thousands of scientific studies have since been conducted, numerous government hearings have been held, and veterans organizations have pressed for conclusive answers, but the question of the health effects of herbicide exposure in Vietnam remains shrouded in controversy and mistrust. Indeed some veterans organizations, researchers, and public interest organizations remain skeptical that the issue has received full and impartial consideration by the Department of Veterans Affairs (DVA; formerly the Veterans Administration) and other federal agencies.

Faced with this lingering uncertainty and demands that the concerns of veterans be adequately addressed, the U.S. Congress passed Public Law 102-4, the "Agent Orange Act of 1991." This legislation directed the Secretary of Veterans Affairs to request that the National

Academy of Sciences conduct a comprehensive review and evaluation of available scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and their components, including dioxin.

In February 1992, the Institute of Medicine (IOM) of the National Academy of Sciences signed an agreement with the DVA to review and summarize the strength of the scientific evidence concerning the association between herbicide exposure during Vietnam service and each disease or condition suspected to be associated with such exposure. The IOM was also asked to make recommendations concerning the need, if any, for additional scientific studies to resolve areas of continuing scientific uncertainty and to comment on four particular programs mandated in Public Law 102-4.

To carry out the study, the IOM established the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. In conducting its study, the committee operated independently of the DVA and other government agencies. The committee was not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure; this was not part of its congressional charge. Rather, the study provides scientific information for the Secretary of Veterans Affairs to consider as the DVA exercises its responsibilities to Vietnam veterans.

ORGANIZATION AND FRAMEWORK

The framework for this report reflects the size and complexity of the committee's task. The committee felt that an evaluation of the health effects of exposure to herbicides in Vietnam veterans would not be complete without a historical review of the Agent Orange controversy. The report begins in Chapter 2 by tracing more than two decades of public concern about the military use of herbicides during the war in Vietnam, in addition to public concern over various environmental and occupational exposures to herbicides and dioxin that arose in parallel to veterans' concerns, and describes federal and state responses to this national dilemma.

Chapter 3 provides background information on the nature and extent of potential exposure of Vietnam veterans to herbicides, based on information about the military herbicide program. Some 3 million military personnel served in or near Vietnam, and as one historian notes, "there was no 'typical' U.S. soldier in Vietnam . . . Americans who served there went through many varied experiences–partly because the quality of the war varied in different areas of the country, and partly because the nature changed over time" (Karnow, 1991). Individual experiences also varied by branch of service, military occupation, rank, and type of military unit. As reflected in military records, the use of herbicides was varied as well. Starting in 1962 and peaking in the late 1960s, seven different herbicide formulations were used in varying quantities for a variety of purposes in different parts of the country; approximately 65 percent of these herbicides were contaminated by TCDD, in varying concentrations. Aerial spraying of herbicides by Operation Ranch Hand accounted for approximately 86 percent of all spraying and was well documented; other spraying by helicopters and from trucks or backpacks was poorly documented.

Chapter 4 provides toxicological background on the biologic plausibility of health effects that may occur in humans after accidental or occupational exposure to herbicides and TCDD components. This chapter describes the biological and chemical properties of the compounds in question as determined by basic research and animal studies. TCDD administered to laboratory animals interacts with an intracellular protein called the Ah receptor. This interaction appears to play a role in a number of health effects observed in animals. Because humans also have intracellular proteins that have been identified as Ah receptors, it is plausible that interactions between TCDD and these receptors could play a role in human health effects. In contrast to TCDD, the effects of the herbicides do not appear to be mediated through interactions with intracellular receptors. TCDD has also been shown to have a wide range of effects in laboratory animals on growth regulation, hormone systems, and other factors associated with the regulation of activities in normal cells. In addition, TCDD has been shown to cause cancer in laboratory animals at a variety of sites. If TCDD has similar effects on cell regulation in humans, it is plausible that it could have an effect on human cancer incidence. In contrast to TCDD, there is no convincing evidence in animals of, or mechanistic basis for, carcinogenicity or other health effects of any of the herbicides, although they have not been studied as extensively as TCDD.

In fulfilling its charge of judging whether each of a set of human health effects is associated with exposure to herbicides or dioxin, most of the committee's efforts concentrated on reviewing and interpreting epidemiologic studies. The committee began its evaluation presuming neither the existence nor the absence of association. It has sought to characterize and weigh the strengths and limitations of the available evidence. These judgments have both quantitative and qualitative aspects. They reflect the nature of the exposures, health outcomes, and populations at issue; the characteristics of the evidence examined; and the approach taken to evaluate that evidence. To facilitate independent assessment of the committee's conclusions, Chapter 5 describes as explicitly as possible the methodological considerations that guided the committee's review and its process of evaluation.

In reviewing the literature, the committee discerned that the existing epidemiologic data base is severely lacking in quantitative measures of individual exposure to herbicides and dioxin. Assessment of the intensity and duration of individual exposures is a key component in determining whether specific health outcomes are associated with exposure to dioxin or other chemicals found in the herbicides used in Vietnam. Although different approaches have been used to estimate exposure in Vietnam veterans and in others exposed occupationally or environmentally, each approach is limited in its ability to determine precisely the degree and level of individual exposure. The problems associated with each of these approaches are discussed in detail in Chapter 6. New biochemical techniques that can detect small amounts of TCDD in the blood many years after exposure have some merit, especially for detecting *group* differences. However, because of common background exposure of all Americans to TCDD, poorly understood variations among individuals in TCDD metabolism, and relatively large measurement errors, *individual* TCDD serum levels are usually not meaningful. Furthermore, because not all herbicides used in Vietnam contained TCDD, serum TCDD levels are not good indicators of overall exposure to herbicides. Chloracne has been used in epidemiologic studies

as a biomarker for TCDD exposure, but the data indicate that it is neither sensitive nor specific. It is usually not long lasting, is difficult to diagnose, and is not at all sensitive to exposure to herbicides that are not contaminated with TCDD.

Although definitive data are lacking, the available quantitative and qualitative evidence about herbicide exposure summarized in Chapter 6 suggests that Vietnam veterans as a group had substantially lower exposure to herbicides and dioxin than the subjects in many occupational studies. The participants in Operation Ranch Hand are an exception to this pattern, and it is likely that others among the approximately 3 million men and woman who served in Vietnam were exposed to herbicides at levels associated with health effects. Thus, in the committee's judgment, a sufficiently large range of exposures may exist among Vietnam veterans to conduct a valid epidemiologic study for certain health outcomes (see research recommendations below).

Due, in part, to the uncertain validity of exposure measurements in many of the studies of veterans, the committee decided to review studies of other groups potentially exposed to the herbicides used in Vietnam and TCDD, especially phenoxy herbicides, including 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-T, chlorophenols, and other compounds. These groups include chemical production and agricultural workers, residents of Vietnam, and people exposed heavily to herbicides or dioxins as a result of residing near the site of an accident or a toxic waste dumping area. The committee felt that considering studies of other groups could help address the issue of whether these compounds might be associated with particular health outcomes, even though these results would have only an indirect bearing on the increased risk of disease in veterans themselves. Some of these studies, especially those of workers in chemical production plants, provide stronger evidence about health effects than studies of veterans because exposure was generally more easily quantified and measured. Furthermore, the general level and duration of exposure to the chemicals were greater and the studies were of sufficient size to examine the health risks among those with varying levels of exposure.

Because the committee relied on many of the same epidemiologic studies when assessing potential associations with various health effects, Chapter 7 provides a framework for the methods used in the epidemiologic studies on which the committee based its report. The nature of the exposure to herbicides and herbicide components varied substantially for each; therefore, both the organization of the chapter (which is structured to reflect similarities and differences in the populations studied) and the methodologic issues that are summarized for each study emphasize exposure.

CONCLUSIONS ABOUT HEALTH OUTCOMES

Chapters 8 through 11 provide a detailed review of the epidemiologic studies evaluated by the committee and their implications for cancer, reproductive, neurobehavioral, and other health effects. The committee's specific mandate was to determine, if possible,

1. whether there is a statistical association between the suspect diseases and herbicide use, taking into account the strength of the scientific evidence and the appropriateness of the methods used to detect the association;

2. the increased risk of disease among individuals exposed to herbicides during service in Vietnam; and

3. whether there is a plausible biologic mechanism or other evidence of a causal relationship between herbicide exposure and a disease.

As detailed in Chapter 5, the committee addressed the first part of this charge by assigning each of the health outcomes under study into one of the four categories listed in Table 1-1 on the basis of the epidemiologic evidence that it reviewed. The specific rationale for each of the findings summarized in this table is given in Chapters 8 through 11. The second part of the charge is addressed at the end of this section. The committee's response to the third part of the charge is summarized in general terms in Chapter 4, and specific findings for each health outcome are also given in Chapters 8 through 11.

The definitions of the categories and the criteria for assigning a particular health outcome to them are described in Table 1-1. Consistent with the charge to the Secretary of Veterans Affairs in Public Law 102-4, the distinctions between categories are based on "statistical association," not on causality, as is common in scientific reviews. The committee was charged with reviewing the scientific evidence, rather than making recommendations regarding DVA policy, and Table 1-1 is not intended to imply or suggest any policy decisions, which must rest with the Secretary.

Health Outcomes with Sufficient Evidence of an Association

The committee found sufficient evidence of an association with herbicides and/or TCDD for three cancers: soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. For cancers in this category, a positive association between herbicides and the outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regards evidence from several small studies that are free from bias and confounding, and show an association that is consistent in magnitude and direction, as sufficient evidence for an association.

Soft tissue sarcomas are a rare but diverse group of tumors that share a common International Classification of Diseases code but have a wide variety of forms and causes. The strongest evidence for an association between STS and exposure to phenoxy herbicides comes from a series of case-control studies involving a total of 506 cases conducted by Hardell and colleagues in Sweden (Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell and Eriksson, 1988; Eriksson et al., 1990; Wingren et al 1990) that show an association between

TABLE 1-1 Summary of Findings in Occupational, Environmental, and Veterans Studies Regarding the Association Between Specific Health Problems and Exposure to Herbicides

Sufficient Evidence of an Association

Evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence for an association. There is sufficient evidence of an association between exposure to herbicides and the following health outcomes:

Soft tissue sarcoma
Non-Hodgkin's lymphoma
Hodgkin's disease
Chloracne
Porphyria cutanea tarda (in genetically susceptible individuals)

Limited/Suggestive Evidence of an Association

Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent. There is limited/suggestive evidence of an association between exposure to herbicides and the following health outcomes:

Respiratory cancers (lung, larynx, trachea)
Prostate cancer
Multiple myeloma

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency. There is inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and the following health outcomes:

Hepatobiliary cancers
Nasal/nasopharyngeal cancer
Bone cancer
Female reproductive cancers (breast, cervical, uterine, ovarian)
Renal cancer
Testicular cancer
Leukemia
Spontaneous abortion
Birth defects
Neonatal/infant death and stillbirths
Low birthweight
Childhood cancer in offspring
Abnormal sperm parameters and infertility

TABLE 1-1 (continued)

Inadequate/Insufficient Evidence to Determine Whether an Association Exists (continued)

Cognitive and neuropsychiatric disorders
Motor/coordination dysfunction
Peripheral nervous system disorders
Metabolic and digestive disorders (diabetes, changes in liver enzymes, lipid abnormalities, ulcers)
Immune system disorders (immune modulation and autoimmunity)
Circulatory disorders
Respiratory disorders

Limited/Suggestive Evidence of No Association

Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. *In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.* There is limited/suggestive evidence of *no* association between exposure to herbicides and the following health outcomes:

Skin cancer
Gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, rectal cancer)
Bladder cancer
Brain tumors

NOTE: "Herbicides" refers to the major herbicides used in Vietnam: 2,4-D (2,4-dichlorophenoxyacetic acid); 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and its contaminant TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin); cacodylic acid; and picloram. The evidence regarding association is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

STS and exposure to phenoxy herbicides, chlorophenols, or both. Although these studies have been criticized, the committee feels that there is insufficient justification to discount the consistent pattern of elevated risks, and the clearly described and sound methods employed. These findings are supported by a significantly increased risk in the NIOSH study (SMR=9.2, CI 1.9-27.0) for the production workers most highly exposed to TCDD (Fingerhut et al., 1991), and a similar increased risk in the IARC cohort (SMR=6.1, CI 1.7-15.5) for deaths that occurred between 10 and 19 years after the first exposure (Saracci et al., 1991). These are the two largest, as well as the most highly exposed occupational cohorts. Some studies in other occupational, environmental, and veterans groups showed an increased risk for STS, but the results were commonly nonsignificant possibly because of small sample sizes related to the relative rarity of STS in the population. Because of difficulties in diagnosing this group of tumors, the epidemiologic studies reviewed by the committee were inconsistent with regard to the specific types of tumors included in the analyses. The available data did not permit the committee to determine whether specific forms of STS were or were not associated with TCDD and/or herbicides. Therefore, the committee's findings relate to the class as a whole.

Non-Hodgkin's lymphoma includes a group of malignant lymphomas, that is, neoplasms derived from lymphoreticular cells in lymph nodes, bone marrow, spleen, liver, or other sites in the body. One large, well-conducted case-control study in Sweden by Hardell and colleagues (1981) examined NHL and Hodgkin's disease together and found an odds ratio of 6.0 (CI 3.7-9.7) based on 105 cases for exposure to phenoxy acids or chlorophenols, and these results held up under further investigation of the validity of exposure assessment and other potential biases (Hardell, 1981). A more recent case-control study by Persson and colleagues (1989) showed increased risk for NHL in those exposed to phenoxy acids (OR=4.9, CI 1.0-27.0), based on a logistic regression analysis of 106 cases. Other studies of farmers and agricultural workers are generally positive for an association between NHL and herbicides/TCDD; however, only some are significant. All of the studies of U.S. agricultural workers reviewed showed elevated relative risks (although none were significant), and two NCI studies of farmers in Kansas and Nebraska (Hoar et al., 1986; Zahm et al., 1990) show patterns of increased risk linked to use of 2,4-D. The CDC Selected Cancers Study found an increased risk of NHL in association with service in Vietnam; other studies of veterans, generally with small sample sizes, are consistent with an association. In contrast, studies of production workers, including the largest, most heavily exposed cohorts (Fingerhut et al., 1991; Saracci et al., 1991; Zober et al., 1990; Manz et al., 1991) indicate no increased risk. Thus, unlike most of the other cancers studied by the committee for which the data do not distinguish between the effects of herbicides and TCDD, the available epidemiologic data suggest that the phenoxy herbicides, including 2,4-D, rather than TCDD may be associated with non-Hodgkin's lymphomas.

Hodgkin's disease, also a malignant lymphoma, is a neoplastic disease characterized by progressive anemia and enlargement of lymph nodes, spleen, and liver. Fewer studies have been conducted of HD in relation to exposure to herbicides or TCDD than have been conducted of STS or NHL, but the pattern of results is strikingly consistent. The 60 HD cases in the study by Hardell and colleagues (1981) were later examined by Hardell and Bengtsson (1983),

who found odds ratios of 2.4 (CI 0.9-6.5) for low-grade exposure to chlorophenols and 6.5 (CI 2.7-19.0) for high-grade exposures. Persson and colleagues' study (1989) of 54 HD cases showed a large, but not statistically significant, OR=3.8 (CI 0.5-35.2) for exposure to phenoxy acids. Furthermore, nearly all of the 13 case-control and agricultural worker studies show increased risk for HD, although only a few of these results are statistically significant. As with NHL, even the largest studies of production workers exposed to TCDD do not indicate an increased risk. The few studies of HD in Vietnam veterans tend to show elevated risks, all but one are not statistically significant.

When these three cancers (STS, NHL, and HD) are considered as a whole, it is noteworthy that the strongest evidence for an association with exposure to phenoxy herbicides is the series of case-control studies conducted by Hardell and colleagues and the cohort studies of herbicide applicators and agricultural workers. Studies in other countries are sometimes positive, but not as consistently. Whether this reflects higher typical exposure levels in workers in the countries studied, genetic differences in susceptibility to these diseases, the fact that more intensive studies have taken place, or other risk factors is not known. With regard to STS, the study of Woods and colleagues (1987) suggests that both exposure levels and genetic differences are at play. However, although there may be differences from population to population in the increased risk associated with exposure to herbicides and TCDD, the committee regards the available evidence as sufficient to indicate that there is a statistical association between the herbicides used in Vietnam and STS, NHL, and HD.

The other two health outcomes for which the committee found sufficient evidence of an association with herbicides or TCDD are both skin conditions (see Chapter 11). Chloracne is a specific acne-like skin disorder characterized by exposure to TCDD or related chemicals (but not herbicides). Porphyria cutanea tarda (PCT), which is characterized by thinning and blistering of the skin in sun-exposed areas, is an uncommon disease in which porphyrins are abnormally metabolized. Only genetically predisposed individuals have been shown to develop PCT after TCDD exposure. Both chloracne and PCT have been shown in animal and human studies to be associated with TCDD per se. The clinical evidence for these conditions suggests that onset occurs soon after exposure to TCDD; however, the conditions subside (although perhaps slowly) after exposure ceases.

Health Outcomes with Limited/Suggestive Evidence of An Association

The committee found limited/suggestive evidence of an association for three other cancers: respiratory cancers, prostate cancer, and multiple myeloma. For outcomes in this category, the evidence must be suggestive of an association between herbicides and the outcome, but may be limited because chance, bias, or confounding could not be ruled out with confidence. Typically, at least one high-quality study indicates a positive association, but the results of other studies may be inconsistent.

Among the many epidemiologic studies of respiratory cancers (specifically cancers of the lung, larynx, and trachea), positive associations were found consistently only in those studies in

which TCDD or herbicide exposures were probably high and prolonged, especially the largest, most heavily exposed cohorts of chemical production workers exposed to TCDD (Zober et al., 1990; Fingerhut et al., 1991; Manz et al., 1991; Saracci et al., 1991) and herbicide applicators (Axelson and Sundell, 1974; Riihimaki et al., 1982; Blair, 1983; Green, 1991). Studies of farmers tended to show a decreased risk of respiratory cancers (perhaps due to lower smoking rates), and studies of Vietnam veterans are inconclusive. The committee felt that the evidence for this association was limited/suggestive rather than sufficient because of the inconsistent pattern of positive findings across populations with various degrees of exposure and because the most important risk factor for respiratory cancers--cigarette smoking--was not fully controlled for or evaluated in all studies.

Several studies have shown elevated risk for prostate cancer in agricultural or forestry workers. In a large cohort study of Canadian farmers (Morrison et al., 1993), an increased risk of prostate cancer was associated with herbicide spraying, and increasing risk was shown with increasing number of acres sprayed. For the entire cohort, the relative risk for prostate cancer and spraying at least 250 acres was 1.2 (CI 1.0-1.5). When the analysis was restricted to the farmers most likely to be exposed to phenoxy herbicides or other herbicides, and those with no employees, no custom workers to do the spraying for them, and age between 45-69 years, the test for trend over increasing number of acres sprayed was significant. The risk was elevated a study of USDA forest conservationists (PMR=1.6, CI 0.9-3.0) (Alavanja et al., 1989), and a case-control study of white male Iowans who died of prostate cancer (Burmeister et al., 1983) found a significant association (OR=1.2) that was not associated with any particular agricultural practice. These results are strengthened by a consistent pattern of nonsignificant elevated risks in studies of chemical production workers in the United States and other countries, agricultural workers, pesticide applicators, paper and pulp workers, and the Seveso population. Studies of prostate cancer among Vietnam veterans or following environmental exposures have not consistently shown an association. However, prostate cancer is generally a disease of older men, and the risk among Vietnam veterans would not be detectable in published epidemiologic studies. Because there was a strong indication of a dose-response relationship in one study and a consistent positive association in a number of others, the committee felt that the evidence for association with herbicide exposure was limited/suggestive for prostate cancer.

Multiple myeloma, a cancer of specific bone marrow cells, has been less extensively studied than other lymphomas, but a consistent pattern of elevated risks appears in the studies that have been conducted. Ten studies of agricultural and forestry workers provide information on MM risk in relation to herbicide or pesticide exposure. All demonstrated an odds ratio or SMR greater than 1.0; seven did so at a statistically significant level. This finding is made more specific for herbicide exposure by subanalyses in four of these studies (Burmeister et al., 1983; Cantor and Blair, 1984; Alavanja et al., 1989; Boffetta et al., 1989) that suggest higher risks for those exposed to herbicides, and higher risks for the studies of herbicide applicators (Riikimaki et al., 1983; Swaen et al., 1992). The committee determined that the evidence for this association was limited/suggestive because the individuals in the existing studies--mostly farmers--have, by the nature of their occupation, probably been exposed to a range of

potentially carcinogenic agents other than herbicides and TCDD. Multiple myeloma, like non-Hodgkin's lymphoma and Hodgkin's disease for which there is stronger epidemiologic evidence of an association, is derived from lymphoreticular cells, which adds to the biologic plausibility of an association.

Health Outcomes with Limited/Suggestive Evidence of No Association

For a small group of cancers the committee found a sufficient number and variety of well-designed studies to conclude that there is limited/suggestive evidence of *no* association between these cancers and TCDD or the herbicides under study. This group includes gastrointestinal tumors (colon, rectal, stomach, and pancreatic), skin cancer, brain tumors, and bladder cancer. For outcomes in this category, several adequate studies covering the full range of levels of exposure that human beings are known to encounter are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure, and which have relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

The data on colon cancer exemplify the situation that led the committee to say that there was evidence of no association between a cancer and exposure to herbicides and/or TCDD. Colon cancer is relatively common, so an increase in the risk of these cancers would be relatively easy to detect in occupational studies. The epidemiologic studies reviewed by the committee that address colon cancer include a mixture of occupational studies of various types, environmental studies, and studies of Vietnam veterans. Some of the studies such as the NIOSH (Fingerhut et al., 1991) and IARC (Saracci et al., 1991) cohorts are large and have relatively high exposures. The number of studies with estimated relative risks above and below 1.0 are roughly evenly distributed, and a number of studies have tight confidence intervals that include 1.0. The NIOSH study, for instance, based on 25 exposed cases, finds an odds ratio of 1.2 with a 95 percent confidence interval of 0.8 to 1.8. The IARC study finds an odds ratio of 1.1 (CI 0.8-1.5) based on 41 cases. Thus, this pattern suggests that there is no association between herbicides/TCDD and colon cancer, at least in the situations represented in the available studies.

Health Outcomes with Inadequate/Insufficient Evidence to Determine Whether an Association Exists

The scientific data for the remainder of the cancers and other diseases reviewed by the committee were inadequate or insufficient to determine whether an association exists. For cancers in this category, the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association.

For example, studies fail to control for confounding or have inadequate exposure assessment.

This group includes hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers (breast, cervical, uterine, ovarian), renal cancer, testicular cancer, and leukemia. For example, there are relatively few occupational, environmental, or veterans studies of liver cancer, and most of these are small in size and have not controlled for life-style-related risk factors. One of the largest studies (Hardell et al., 1984) indicates an increased risk for liver cancer and exposure to herbicides, but another study of Swedish agricultural workers (Wiklund, 1983) estimates a relative risk that is significantly less than 1.0. The estimated relative risks from other studies are both positive and negative. As a whole, when bearing in mind the methodological difficulties associated with most of the few existing studies, the evidence regarding liver cancer is not convincing about either an association with herbicides/TCDD or the lack of an association.

The epidemiologic evidence for an association between exposure to herbicides and leukemia comes primarily from studies of farmers and residents of Seveso, Italy. The observed overall relative risk for leukemia mortality and incidence in Seveso was elevated, but not significantly. A number of studies of farmers that the committee found convincing for NHL, HD, or MM also show a consistently elevated risk of leukemia, but these results are not necessarily due to herbicide use because confounding exposures were not controlled for adequately in the analyses of these studies and because when farmers are stratified by suspected use of herbicide, the incidence of leukemia is generally not elevated. Some studies of chemical workers found an increased risk of leukemia, but the number of cases was small in all of these studies. The available data on Vietnam veterans are generally not conclusive because the exposure data are inadequate for the cohort being studied. Small sample sizes weaken the studies of the Ranch Hands or Chemical Corps, where excesses are not likely to be detected.

A number of occupational, environmental, and Vietnam veteran studies were available for assessing the association between herbicide and TCDD exposures and reproductive outcomes. These studies generally reported no association with any of the reproductive outcomes examined by the committee–spontaneous abortion, birth defects, stillbirth, neonatal and infant death, low birthweight, childhood cancer, or altered sperm parameters and infertility. However, given the small sample sizes, the lack of consistent findings, and inadequate exposure classification in most studies, the evidence is considered inadequate for determination of an association.

Studies of neurotoxic effects of herbicides or TCDD were also inadequate for determining whether an association exists between exposures and chronic cognitive or neuropsychiatric disorders, motor/coordination dysfunction, and peripheral nervous system disorders. As a group the studies have not applied uniform operational definitions of neurobehavioral disorders. Information on individual exposure was often inadequate and complicated by exposure to multiple chemicals, and only a limited number of studies provided sufficient comparison group data. Reported abnormalities have ranged from mild and reversible to severe and chronic. While the chances of detecting subtle central nervous system disorders 20 years after exposure are small given the assessment tools currently available, the committee recognized that it may be possible for subtle changes that occurred earlier in life to manifest themselves in later adult

life when compounded by the normal aging process. Therefore, while the currently available evidence is insufficient, study of the interactive effects of exposure to herbicides and TCDD with age on neurobehavioral functioning are encouraged. In addition, observations from followup of veterans and some environmental studies warrant further investigation of motor/sensory/coordination problems in exposed persons.

Other health effects examined by the committee for which the evidence was determined to be insufficient included several metabolic and digestive disorders (diabetes, changes in liver enzymes, lipid abnormalities, and gastrointestinal ulcers), immune system disorders, and circulatory and respiratory disorders. Assessment of these disorders in association with herbicides and TCDD involved the medical evaluation of a wide array of critical signs and symptoms, laboratory parameters, and other diagnostic tools. Studies of these health effects were limited by poor exposure measures, generally small sample sizes, and the lack of assessment of independent risk factors for certain outcomes, such as smoking and certain circulatory and respiratory disorders, or alcohol use and ulcers.

Increased Risk in Vietnam Veterans

Although there have been numerous health studies of Vietnam veterans, most have been hampered by relatively poor measures of exposure to herbicides or TCDD, in addition to other methodological problems. In Table 1-1, most of the evidence on which the findings are based comes from studies of people exposed to dioxin or herbicides in occupational and environmental settings, rather than from studies of Vietnam veterans. The committee found this body of evidence sufficient for reaching the conclusions about statistical associations between herbicides and health outcomes summarized in Table 1-1; however, the lack of adequate data on Vietnam veterans per se complicates the second part of the committee's charge, which is to determine the increased risk of disease among individuals exposed to herbicides during service in Vietnam. To estimate the magnitude of risk for a particular health outcome among herbicide-exposed Vietnam veterans, quantitative information about the dose-time-response relationship for each health outcome in humans, information on the extent of herbicide exposure among Vietnam veterans, and estimates of individual exposure are needed. Given the large uncertainties that remain about the magnitude of potential risk from exposure to herbicides in the studies that have been reviewed (Chapters 8-11), the inadequate control for important confounders, and the uncertainty about the nature and magnitude of exposure to herbicides in Vietnam (Chapter 6), none of the ingredients necessary for a quantitative risk assessment are available. Thus, it is not possible for the committee to quantify the degree of risk likely to be experienced by veterans because of their exposure to herbicides in Vietnam. The available quantitative and qualitative evidence about herbicide exposure among various groups studied suggests that Vietnam veterans as a group (except those with documented high exposures, such as participants in Operation Ranch Hand) had lower exposure to herbicides and TCDD than the subjects in many occupational and environmental studies. However, individual

veterans who had very high exposures to herbicides could have risks approaching those in the occupational and environmental studies.

RESEARCH RECOMMENDATIONS

The committee was also asked to make recommendations concerning the need, if any, for additional scientific studies to resolve areas of continuing scientific uncertainty concerning the health effects of the herbicides used in Vietnam. Based on its review of the available epidemiologic evidence and a consideration of the quality of exposure information available in existing studies, especially of Vietnam veterans, the committee concluded that a series of epidemiologic studies of veterans could yield valuable information if a new, valid exposure reconstruction model could be developed. The committee also sees value in continuing the existing Ranch Hand study and expanding it to include Army Chemical Corps veterans. The committee's research recommendations emphasize studies of Vietnam veterans, rather than general toxicologic or epidemiologic studies of occupationally or environmentally exposed populations. A substantial amount of research on the toxicology and epidemiology of herbicides and herbicide components is already under way in the United States and abroad. Indeed, many of the studies on which the committee's conclusions are based have been published since 1991. Although not targeted specifically to Vietnam veterans, it is likely that this research will also contribute to the knowledge of potential health effects in this population.

Epidemiologic Studies of Vietnam Veterans

The committee makes the following recommendations regarding epidemiologic studies of Vietnam veterans.

Recommendation 1. The committee endorses continued follow-up of the Air Force Ranch Hand cohort and its comparison group, and recommends that members of the Army Chemical Corps and an appropriate comparison group be followed in a similar study. An independent, nongovernmental scientific panel should be established to review and approve a new, expanded research protocol for both study populations, and to commission and direct a common analysis of the results.

Much can be learned by reanalysis of existing data or more in-depth analysis of data expected from current research programs investigating the health of Vietnam veterans, including the Air Force Ranch Hand study and DVA studies of other highly exposed Vietnam veterans such as members of the Chemical Corps. Priorities for specific health outcomes are

discussed after recommendation 6. Public perception of the federal government's interest in the outcome of these studies suggests the need for studies of the health of Vietnam veterans to be conducted by a nongovernmental organization. Ranch Hand's excellent participation rate argues that components of the Department of Defense or the DVA continue to conduct follow-up examinations of the Ranch Hand and Army Chemical Corps cohorts. However, an independent, nongovernmental scientific panel is needed to oversee the analyses of resulting data in order to satisfy the public's concern about impartiality and scientific credibility.

As discussed in Chapter 6, one of the major problems with the interpretation of existing studies is the frequent lack of appropriate measures of exposure to herbicides or TCDD; however, the committee finds that it may be possible to develop better exposure measures for Vietnam veterans. In particular, Chapter 6 proposes measures that are not dependent on serum TCDD levels (which the committee finds inappropriate for the full range of herbicide exposures) but instead recommends the use of less formal sources of historical information about base perimeter spraying and other relevant exposures, as discussed below in Recommendation 4. Thus, the committee concludes that certain further research efforts using new measures of exposure to herbicides in Vietnam are both necessary and potentially feasible. However, each of the possible measures that the committee has considered involves some degree of nondifferential misclassification bias, and the effect of this bias on risk estimates would likely be to underestimate true effects if they existed, possibly to the point that they would not be detected. In particular, the committee recommends that the following steps be taken prior to undertaking new epidemiologic studies of Vietnam veterans, for the reasons described below.

Recommendation 2. The Department of Defense and the Department of Veterans Affairs should identify Vietnam service in the computerized index of their records.

Chapter 3 notes that Vietnam service is not a "flagged item" on the computerized index of military personnel records archived at the National Personnel Records Center, which is maintained by the General Services Administration, under an agreement with the Department of Defense, in St. Louis, Missouri. Therefore, the computerized index of the record system does not allow for searches or selection of records of individuals who have served in Vietnam. The lack of an indicator of Vietnam service complicates every epidemiologic study of veterans based on military records and leads to methodologic inconsistencies among studies in defining the population under consideration. Adding this indicator to the computerized data base would facilitate future mortality studies based on computerized records, thereby increasing accuracy and decreasing cost, and would also simplify other epidemiologic studies of health outcomes in Vietnam veterans. All servicemen and women who were stationed in Vietnam or in the Vietnam theater during the Vietnam era should be identified in the records.

Recommendation 3. Biomarkers for herbicide exposure should be developed further.

Considerable uncertainty remains about the use of current or future serum TCDD levels as indicators of past exposure to dioxin in Vietnam veterans. Further research on the toxicokinetics of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) is needed to permit more accurate extrapolation from current serum TCDD measurements to past exposures. Development of new biomarkers for exposure to herbicides, per se, also would be useful.

Recommendation 4. A nongovernmental organization with appropriate experience in historical exposure reconstruction should be commissioned to develop and test models of herbicide exposure for use in studies of Vietnam veterans.

Exposure assessment has been a weak aspect of most epidemiologic studies of Vietnam veterans. The military reports and personal testimony reviewed by the committee suggest that a sufficient range of exposure to herbicides may exist among Vietnam veterans for valid epidemiologic studies of certain health outcomes, and the committee believes that it is possible to develop valid exposure reconstruction models for such studies by using the methods of historical exposure reconstruction. Historical exposure reconstruction requires substantial professional judgment, and the results might be questioned if developed by a government agency; therefore, the committee recommends that the DVA arrange for a nongovernmental organization with appropriate experience in historical exposure reconstruction to develop and test potential models of herbicide exposure for use in studies of Vietnam veterans.

Recommendation 5. The exposure reconstruction models developed according to Recommendation 4 should be evaluated by an independent, nongovernmental scientific panel established for this purpose.

Herbicide exposure reconstruction models for Vietnam veterans must be thoroughly evaluated before epidemiologic studies based on these models proceed. The committee has identified three possible approaches to such an evaluation, which are discussed in more detail in Chapter 6: (1) internal consistency checks, (2) comparisons of exposure measures based on the reconstruction model with actual serum dioxin measurements, and (3) assessments of the association between exposure reconstruction measures and health outcomes shown in occupational or environmental studies to be associated with herbicides. Scientific judgment is required in interpreting the results of such an evaluation, so the committee cannot specify explicit criteria for acceptance or rejection of the new exposure reconstruction models in advance of their development and testing. Thus, the committee recommends that an independent, nongovernmental scientific panel be established to review the results of the proposed evaluation studies and to judge the validity and feasibility of the exposure reconstruction models. This panel should have expertise in historical exposure reconstruction

and in epidemiology. In order to maintain the public and scientific credibility of the study, the panel members should be nongovernmental and independent of the organization that develops the exposure reconstruction models.

Recommendation 6. If the scientific panel proposed in Recommendation 5 determines that a valid exposure reconstruction model is feasible, the Department of Veterans Affairs and other government agencies should facilitate additional epidemiologic studies of veterans.

A number of possible epidemiologic studies could provide additional information on the health effects of exposure to herbicides in Vietnam beyond what is already known. Highest research priority should be given to those health effects for which additional study is likely to change the balance of the evidence for or against an association. This includes

a. health outcomes for which current evidence is limited/suggestive of an association (lung and respiratory cancers, multiple myeloma, and prostate cancer);
b. health outcomes for which current evidence is insufficient or inadequate to determine whether an association exists, but which, in the committee's judgment, are plausible based on animal toxicologic data (such as nasal/nasopharyngeal cancer) or for which there are known associations with related chemical compounds in humans (such as liver cancer and polychlorinated biphenyls; Nicholson, 1987);
c. health outcomes for which the typical age at onset has not yet been reached by members of the Vietnam veteran cohort (such as prostate cancer).

The committee also recommends that priority be given to additional research on reproductive effects that would help clarify the possible effects of herbicides. In particular, the committee believes that extensive reanalysis of the Ranch Hand reproductive data could shed additional light on these questions (see Chapter 9 and Appendix C).

Although there is sufficient evidence of an association between occupational or environmental exposures to herbicides and non-Hodgkin's lymphoma, Hodgkin's disease, and soft tissue sarcomas, the existing information on dose-response relationships is incomplete, especially with regard to Vietnam veterans. If a valid exposure reconstruction method can be developed, it might be applied to the exposure data available from existing case-control studies to provide additional dose-response evaluations. Additional refinement of the clinical and pathological definitions of soft tissue sarcomas in epidemiologic studies would also help to determine which of the specific cancers in this class are associated with herbicides or TCDD.

The committee recognizes that the recommendations for development of a historical exposure reconstruction model and its use in epidemiologic studies might seem at variance with the Centers for Disease Control (CDC), White House Agent Orange Working Group (AOWG), and Office of Technology Assessment (OTA) conclusions made in 1986 with regard to the congressionally mandated Agent Orange Study. The committee has come to a different conclusion for four reasons: First, the CDC-AOWG-OTA conclusions were based in large part

on serum TCDD measurements, which the committee feels are insufficient for validating exposure to herbicides used in Vietnam, as explained in Chapter 6. Second, the arguments underlying the earlier conclusion that individuals in combat units were widely dispersed and that troop movement data are incomplete imply that exposure measurements may be imprecise, not that they are invalid. However, these arguments do suggest that historical reconstruction of exposure will have nondifferential misclassification errors that will lead to underestimates of the relative risk of health outcomes if an association is in fact present. Third, the committee is proposing the use of more, but less formal, information on exposure than was considered in 1986. This includes the development and use of informal information on perimeter spraying, which might account for more meaningful herbicide exposure than the aerial spraying documented on the HERBS tapes. Finally, the committee does not know whether the approach it proposes will prove valid or whether new methods will identify a sufficient number of highly exposed Vietnam veterans for an epidemiologic study. In the committee's judgment, however, the likelihood that this approach will be successful is sufficient for it to be recommended.

Mandated Research Efforts

For the purposes of further research on the health effects of Vietnam service, Public Law 102-4 mandates that the DVA establish four specific programs that are subject to initiation, continuance, or discontinuation, depending on the findings of this IOM report, and the committee is charged with making recommendations about these specific mandates. The DVA has no specific plans for any of these research efforts beyond the minimal descriptions given in the law, so the committee is able to comment on them in only the broadest terms.

The committee's recommendations speak to its legislative mandate to determine "the feasibility of conducting additional scientific research on" health hazards resulting from exposure to dioxin and herbicides used in Vietnam, the research mandate in section 8 of Public Law 102-4. As previously stated, the committee feels that a series of epidemiologic studies of veterans could yield valuable information if a new, valid exposure reconstruction model can be constructed.

Section 6 of Public Law 102-4 requires the DVA to "compile and analyze, on a continuing basis, all clinical data" that (1) are obtained in connection with DVA examinations and treatment of Vietnam veterans, and (2) are likely to be scientifically useful in determining the association between disabilities experienced by these veterans and exposure to dioxin or herbicides. Such a system, called the Agent Orange Registry (see Chapter 2), currently exists. Section 7 of the law calls for the establishment of a system for the collection and storage of voluntarily contributed samples of blood and tissue of veterans who served in Vietnam. Balancing the strengths and weaknesses of stored biological samples and clinical data for research purposes, the committee feels that systems of this sort have scientific value, but only to the extent that they are components of specific, well-designed studies; see, for instance, National Research Council (1991). In the absence of a clear study design to guide such activities, and without resolution of important design, quality control, and ethical issues

regarding tissue banks, the committee does not recommend the establishment at this time of the clinical data and tissue archiving systems described in sections 6 and 7 of the law.

The final mandate in Public Law 102-4 on which the committee must comment calls for the testing of serum of Vietnam veterans who apply for medical care or file a disability compensation claim for TCDD (section 9). The purpose of this mandate is not stated in the legislation. If research purposes are contemplated, the committee's discussion about tissue archiving systems applies, and such a program would not be recommended at this time. It is also possible that this program is intended to provide information on individual exposure to dioxins or herbicides to aid in individual compensation decisions. The committee cannot make recommendations for DVA policy, but notes that the finding in Chapter 6 that individual TCDD serum levels in Vietnam veterans are usually not meaningful (because of common background exposures to TCDD, poorly understood variations among individuals in TCDD metabolism, relatively large measurement errors, and exposure to herbicides that did not contain TCDD) might apply to this mandate.

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Public Law 102-4
102d Congress

An Act

To provide for the Secretary of Veterans Affairs to obtain independent scientific review of the available scientific evidence regarding associations between diseases and exposure to dioxin and other chemical compounds in herbicides, and for other purposes.

Feb. 6, 1991
[H.R. 556]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Agent Orange Act of 1991
38 USC 101 note

SECTION 1. SHORT TITLE.

This Act may be cited as the "Agent Orange Act of 1991".

SEC. 2. PRESUMPTION OF SERVICE CONNECTION FOR DISEASES ASSOCIATED WITH EXPOSURE TO CERTAIN HERBICIDE AGENTS.

(a) IN GENERAL.—(1) Chapter 11 of title 38, United States Code, is amended by adding at the end of subchapter II the following new section:

"§ 316. Presumptions of service connection for diseases associated with exposure to certain herbicide agents

"(a)(1) For the purposes of section 310 of this title, and subject to section 313 of this title—

"(A) a disease specified in paragraph (2) of this subsection becoming manifest as specified in that paragraph in a veteran who, during active military, naval, or air service, served in the Republic of Vietnam during the Vietnam era; and

"(B) each additional disease (if any) that (1) the Secretary determines in regulations prescribed under this section warrants a presumption of service-connection by reason of having positive association with exposure to an herbicide agent, and (2) becomes manifest within the period (if any) prescribed in such regulations in a veteran who, during active military, naval, or air service, served in the Republic of Vietnam during the Vietnam era and while so serving was exposed to that herbicide agent,

shall be considered to have been incurred in or aggravated by such service, notwithstanding that there is no record of evidence of such disease during the period of such service.

"(2) The diseases referred to in paragraph (1)(A) of this subsection are the following:

"(A) Non-Hodgkin's lymphoma becoming manifest to a degree of disability of 10 percent or more.

"(B) Each soft-tissue sarcoma becoming manifest to a degree of disability of 10 percent or more other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma.

"(C) Chloracne or another acneform disease consistent with chloracne becoming manifest to a degree of disability of 10 percent or more within one year after the last date on which the veteran performed active military, naval, or air service in the Republic of Vietnam during the Vietnam era

"(d) Whenever a disease is removed from regulations prescribed under this section—

"(1) a veteran who was awarded compensation for such disease on the basis of the presumption provided in subsection (a) before the effective date of the removal shall continue to be entitled to receive compensation on that basis; and

"(2) a survivor of a veteran who was awarded dependency and indemnity compensation for the death of a veteran resulting from such disease on the basis of such presumption shall continue to be entitled to receive dependency and indemnity compensation on such basis.

"(e) Subsections (b) through (d) shall cease to be effective 10 years after the first day of the fiscal year in which the National Academy of Sciences transmits to the Secretary the first report under section 3 of the Agent Orange Act of 1991.". Termination date

(2) The table of sections at the beginning of such chapter is amended by inserting after the item relating to section 315 the following new item:

"316. Presumptions of service connection for diseases associated with exposure to certain herbicide agents.".

(b) CONFORMING AMENDMENT.—Section 313 of title 38, United States Code, is amended by inserting "or 316" after "section 312" each place it appears.

SEC. 3. AGREEMENT WITH NATIONAL ACADEMY OF SCIENCES 38 USC 316 note

(a) PURPOSE.—The purpose of this section is to provide for the National Academy of Sciences, an independent nonprofit scientific organization with appropriate expertise which is not part of the Federal Government, to review and evaluate the available scientific evidence regarding associations between diseases and exposure to dioxin and other chemical compounds in herbicides.

(b) AGREEMENT.—The Secretary shall seek to enter into an agreement with the National Academy of Sciences for the Academy to perform the services covered by this section. The Secretary shall seek to enter into such agreement not later than two months after the date of the enactment of this Act.

(c) REVIEW OF SCIENTIFIC EVIDENCE.—Under an agreement between the Secretary and the National Academy of Sciences under this section, the Academy shall review and summarize the scientific evidence, and assess the strength thereof, concerning the association between exposure to an herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era and each disease suspected to be associated with such exposure.

(d) SCIENTIFIC DETERMINATIONS CONCERNING DISEASES.—(1) For each disease reviewed, the Academy shall determine (to the extent that available scientific data permit meaningful determinations)—

(A) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association;

(B) the increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and

(C) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease

National Academy of Sciences. If the Secretary enters into such an agreement with another organization, then any reference in this section and in section 316 of title 38, United States Code (as added by section 2), to the National Academy of Sciences shall be treated as a reference to the other organization.

SEC. 4. OUTREACH SERVICES.

Section 1204(a) of the Veterans' Benefits Improvement Act of 1988 (division B of Public Law 100-687; 102 Stat. 4125) is amended— 38 USC 241 note.

(1) in clause (1), by striking out ", as such information on health risks becomes known";

(2) by redesignating clauses (1) and (2) as clauses (A) and (B), respectively;

(3) by inserting "(1)" after "PROGRAM.—"; and

(4) by adding at the end the following new paragraph:

"(2) The Secretary of Veterans Affairs shall annually furnish updated information on health risks described in paragraph (1)(A) to veterans referred to in paragraph (1).".

SEC. 5. EXTENSION OF HEALTH-CARE ELIGIBILITY BASED ON EXPOSURE TO AGENT ORANGE OR IONIZING RADIATION.

Section 610(e)(3) of title 38, United States Code, is amended by striking out "December 31, 1990" and inserting in lieu thereof "December 31, 1993".

SEC. 6. RESULTS OF EXAMINATIONS AND TREATMENT OF VETERANS FOR DISABILITIES RELATED TO EXPOSURE TO CERTAIN HERBICIDES OR TO SERVICE IN VIETNAM. 38 USC 316 note

(a) IN GENERAL.—Subject to subsections (d) and (e), the Secretary of Veterans Affairs shall compile and analyze, on a continuing basis, all clinical data that (1) is obtained by the Department of Veterans Affairs in connection with examinations and treatment furnished to veterans by the Department after November 3, 1981, by reason of eligibility provided in section 610(e)(1)(A) of title 38, United States Code, and (2) is likely to be scientifically useful in determining the association, if any, between the disabilities of veterans referred to in such section and exposure to dioxin or any other toxic substance referred to in such section or between such disabilities and active military, naval, or air service in the Republic of Vietnam during the Vietnam era.

(b) ANNUAL REPORT.—The Secretary shall submit to the Committees on Veterans' Affairs of the Senate and the House of Representatives an annual report containing—

(1) the information compiled in accordance with subsection (a);

(2) the Secretary's analysis of such information;

(3) a discussion of the types and incidences of disabilities identified by the Department of Veterans Affairs in the case of veterans referred to in subsection (a);

(4) the Secretary's explanation for the incidence of such disabilities;

(5) other explanations for the incidence of such disabilities considered reasonable by the Secretary; and

(6) the Secretary's views on the scientific validity of drawing conclusions from the incidence of such disabilities, as evidenced by the data compiled under subsection (a), about any association between such disabilities and exposure to dioxin or any other

(f) EFFECTIVE DATE.—(1) This section shall take effect at the end of the 90-day period beginning on the date on which the first report of the National Academy of Sciences under section 3(g) is received by the Secretary, except that this section shall not take effect if the Secretary, after receiving that report and before the end of that 90-day period—

(A) determines that it is not feasible or cost-effective to carry out this section or that carrying out this section would not make a material contribution to the body of scientific knowledge concerning the health effects in humans of herbicide exposure; and

(B) notifies the Committees on Veterans' Affairs of the Senate and House of Representatives of the Secretary's determination and the reasons therefor.

(2) In making a determination under this subsection, the Secretary shall give great weight to the views and recommendations of the Academy expressed in that report with respect to the implementation of this section.

SEC. 8. SCIENTIFIC RESEARCH FEASIBILITY STUDIES PROGRAM. 38 USC 316 note

(a) ESTABLISHMENT OF PROGRAM.—Subject to subsections (e) and (f), the Secretary of Veterans Affairs shall establish a program to provide for the conduct of studies of the feasibility of conducting additional scientific research on—

(1) health hazards resulting from exposure to dioxin;

(2) health hazards resulting from exposure to other toxic agents in herbicides used in support of United States and allied military operations in the Republic of Vietnam during the Vietnam era; and

(3) health hazards resulting from active military, naval, or air service in the Republic of Vietnam during the Vietnam era.

(b) PROGRAM REQUIREMENTS.—(1) Under the program established pursuant to subsection (a), the Secretary shall, pursuant to criteria prescribed pursuant to paragraph (2), award contracts or furnish financial assistance to non-Government entities for the conduct of studies referred to in subsection (a). Government contracts Grants

(2) The Secretary shall prescribe criteria for (A) the selection of entities to be awarded contracts or to receive financial assistance under the program, and (B) the approval of studies to be conducted under such contracts or with such financial assistance.

(c) REPORT.—The Secretary shall promptly report the results of studies conducted under the program to the Committees on Veterans' Affairs of the Senate and the House of Representatives.

(d) CONSULTATION WITH THE NATIONAL ACADEMY OF SCIENCES.—(1) To the extent provided under any agreement entered into by the Secretary and the National Academy of Sciences under this Act—

(A) the Secretary shall consult with the Academy regarding the establishment and administration of the program under subsection (a); and

(B) the Academy shall review the studies conducted under contracts awarded pursuant to the program and the studies conducted with financial assistance furnished pursuant to the program.

(2) The agreement shall require the Academy to submit to the Secretary and the Committees on Veterans' Affairs of the Senate and the House of Representatives any recommendations that the

(A) determines that it is not feasible or cost-effective to carry out this section or that carrying out this section would not make a material contribution to the body of scientific knowledge concerning the health effects in humans of herbicide exposure, and

(B) notifies the Committees on Veterans' Affairs of the Senate and House of Representatives of the Secretary's determination and the reasons therefor.

(2) In making a determination under this subsection, the Secretary shall give great weight to the views and recommendations of the Academy expressed in that report with respect to the implementation of this section.

SEC. 10. CONFORMING AMENDMENTS TO PUBLIC LAW 98-542.

(a) AMENDMENTS TO SECTION 2.—Section 2 of Public Law 98-542 (38 U.S.C. 354 note) is amended by striking out "that chloracne," in paragraph (5) and all that follows through "herbicides and".

(b) AMENDMENTS TO SECTION 3.—Section 3 of such Public Law is amended by striking out "during service in the Armed Forces in the Republic of Vietnam to a herbicide containing dioxin or" 38 USC 354 note

(c) AMENDMENTS TO SECTION 5.—Section 5 of such Public Law is amended as follows: 38 USC 354 note

(1) Subsection (a)(1) is amended by striking out "during service—" and all that follows through "in connection with" and inserting in lieu thereof "during service in connection with"

(2) Subsection (b) is amended—

(A) by striking out "of exposure to herbicides containing dioxin or" in the first sentence of paragraph (1)(A);

(B) by striking out "evidence indicating—" in paragraph (2)(B) and all that follows through "(ii) a connection to" and inserting in lieu thereof "evidence indicating a connection to";

(C) in paragraph (3)—

(i) by striking out "herbicide or" in subparagraph (A), and

(ii) by striking out "to a herbicide containing dioxin or" in subparagraph (B); and

(D) by striking out "of the appropriate panel" in the first sentence of paragraph (1)(B), in the first sentence of paragraph (2)(A)(i), and in paragraph (2)(B).

(d) AMENDMENTS TO SECTION 6.—Section 6 of such Public Law is amended as follows: 38 USC 354 note

(1) Subsection (a) is amended—

(A) in the matter preceding paragraph (1), by striking out "fifteen members" and inserting in lieu thereof "nine members";

(B) in paragraph (1)—

(i) by striking out "eleven individuals" and inserting in lieu thereof "six individuals";

(ii) by striking out subparagraph (A);

(iii) by redesignating subparagraph (B) as subparagraph (A); and

(iv) by redesignating subparagraph (C) as subparagraph (B) and in that subparagraph—

(I) by striking out "five individuals" and inserting in lieu thereof "three individuals"; and

(II) by striking out "dioxin or"; and