HUMAN HEALTH EFFECTS
ASSOCIATED WITH EXPOSURE
TO HERBICIDES AND/OR THEIR
ASSOCIATED CONTAMINANTS - CHLORINATED DIOXINS

AGENT ORANGE AND THE VIETNAM VETERAN

A REVIEW OF THE SCIENTIFIC LITERATURE
APRIL, 1990

THE AGENT ORANGE SCIENTIFIC TASK FORCE
working with
THE AMERICAN LEGION
VIETNAM VETERANS OF AMERICA
THE NATIONAL VETERANS LEGAL SERVICES PROJECT
EXECUTIVE SUMMARY

For over a decade, the opponents of disability and death compensation for Vietnam veterans exposed to Agent Orange in the U.S. Congress and the Department of Veterans Affairs have based their opposition on the assertion that there is not enough scientific evidence to show a link between Agent Orange exposure and any disease other than chloracne. The VA is currently conducting a rulemaking proceeding under mandate of a statute and a federal court order that focuses on this very issue.

Because we have been dissatisfied with the efforts of the VA and its Advisory Committee on Environmental Hazards in this rulemaking proceeding, we decided it was essential to a fair resolution of the Agent Orange issue for an independent group of scientists to address the issues currently under consideration by Congress and the VA. We therefore assembled the Agent Orange Scientific Task Force -- a group of prominent, independent scientists who are knowledgeable about the scientific studies concerning the health effects of exposure to dioxin. We asked the Task Force to prepare a report that summarizes its review of the scientific literature related to potential human health effects associated with exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins). In reviewing the scientific literature, we asked the Task Force to determine which adverse health effects, if any, are associated with exposure to dioxin, using the standard the VA and its Advisory Committee have adopted in the rulemaking proceeding.
Following review of the scientific literature, the Task Force concluded there is a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and the following adverse health effects: (1) non-Hodgkin's lymphoma, (2) soft tissue sarcoma, (3) skin disorders/chloracne, (4) subclinical hepatotoxic effects (including secondary coproporphyrinuria and chronic hepatic porphyria), and (5) porphyria cutanea tarda (most likely only in individuals with inherited uroporphyrinogen decarboxylase deficiency). The aggregate interpretation of several sound studies showing a statistically significant association for each of these conditions makes this conclusion inescapable.

Further, the scientific evidence supporting the existence of a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) is at least as strong as the scientific evidence of a lack of the association for the following adverse health effects: (1) Hodgkin's disease, (2) neurologic effects, and (3) reproductive and developmental effects. For each of these health effects, there are sound scientific studies showing statistical significance and strong scientific evidence of an association between exposure and effect. However, a statistically significant association is not as consistently supported for these effects as for the first group of health effects.

The above eight adverse health effects satisfy the VA's test for an association which qualifies for disability compensation, i.e., where the scientific evidence shows that a significant statistical association is "at least as likely as not." 38 C.F.R. § 1.17(d)(1).
The Task Force concluded there are other adverse health effects for which there is sound scientific evidence of an association with exposure, but the evidence does not reach the level of formal statistical significance. Nevertheless, were the Task Force a policy-making body concerned with disability compensation for veterans, it might conclude that compensation was due. However, the Task Force was limited to determining the existence of a significant statistical association, and the limited data available at this time show an association, but not a significant statistical association, between exposure to phenoxyacetic acid herbicides and/or dioxin and the following diseases: leukemias, cancers of the kidney, testis, pancreas, stomach, prostate, colon, hepatobiliary tract, and brain, psychosocial effects, immunological abnormalities, gastrointestinal ulcer, and altered lipid metabolism. Further research should be directed at these associations, and policy-makers, cognizant of the limitations on finding significant statistical associations and of the obligation to give the veteran the benefit of the doubt, would be justified in viewing these disorders in a more conclusive light for the purpose of establishing entitlement to disability compensation.

Finally, the epidemiologic evidence on the associations between exposure and the adverse health effects described above is strongly supported by a wide range of experimental animal studies.

The conclusions reached in this report are based on sound scientific and medical evidence, and they provide the basis for rules and legislation aimed at providing disability compensation to Vietnam veterans for disabilities related to the adverse health effects, outlined in this report, caused or aggravated by exposure to Agent Orange.
THE AGENT ORANGE SCIENTIFIC TASK FORCE

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SUMMARY OF RESULTS

THERE IS A SIGNIFICANT STATISTICAL ASSOCIATION BETWEEN EXPOSURE TO AGENT ORANGE AND:

- NON-HODGKIN’S LYMPHOMA
- SOFT TISSUE SARCOMA
- SKIN DISORDERS/CHLORACNE
- SUBCLINICAL HEPATOTOXIC EFFECTS
- PORPHYRIA CUTANEA TARDA

THE SCIENTIFIC EVIDENCE OF A SIGNIFICANT STATISTICAL ASSOCIATION WITH EXPOSURE TO AGENT ORANGE IS AT LEAST AS STRONG AS THE EVIDENCE OF A LACK OF THE ASSOCIATION FOR THE FOLLOWING ADDITIONAL EFFECTS:

- HODGKIN’S DISEASE
- NEUROLOGIC EFFECTS
- REPRODUCTIVE AND DEVELOPMENTAL EFFECTS
THERE IS SOUND SCIENTIFIC EVIDENCE OF AN ASSOCIATION WITH EXPOSURE TO AGENT ORANGE, BUT THE EVIDENCE DOES NOT REACH THE LEVEL OF FORMAL STATISTICAL SIGNIFICANCE, FOR THE FOLLOWING ADDITIONAL EFFECTS:

LEUKEMIAS
CANCER OF THE KIDNEY
CANCER OF THE TESTIS
CANCER OF THE STOMACH
CANCER OF THE PROSTATE
CANCER OF THE COLON
CANCER OF THE HEPATOBILIARY TRACT
CANCER OF THE BRAIN
PSYCHOSOCIAL EFFECTS
IMMUNOLOGICAL ABNORMALITIES
GASTROINTESTINAL ULCER
ALTERED LIPID METABOLISM
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A review of scientific literature related to potential human health effects associated with exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) has been completed. This review included all studies and publications reviewed to date by the Advisory Committee on Environmental Hazards of the Department of Veterans Affairs, and additional pertinent studies not reviewed to date by the Advisory Committee. References to these publications and studies are included as appendices B-E. This review was directed primarily at assessing adverse health effects in Vietnam veterans which may be associated with exposure to Agent Orange, a phenoxyacetic acid herbicide which was contaminated with dioxin.¹

The Standard Used by the Task Force

This literature review focused on epidemiologic studies of exposed humans and used the standard "significant statistical association" because that is the standard used by the VA’s Advisory Committee. At the outset, it should be made clear that the fact that the Task Force used this standard should not be interpreted to mean that the Task Force believes this is an appropriate standard for basing decisions on Agent Orange.

There are many reasons why use of this standard may be

¹ References in this report to "dioxin," "TCDD," and "2,3,7,8-TCDD" all refer to 2,3,7,8-tetrachlorodibenzo-p-dioxin.
inappropriate. In order for epidemiologic studies to find statistically significant associations between exposure and health effects like cancers, these studies must have sufficient power and sensitivity. This generally requires large numbers of exposed subjects available for study and follow-up for many decades (if not for the lifetime of the subjects). A major problem with the various epidemiologic studies of people exposed to phenoxyacetic acid herbicides is that there have not been many large populations with known exposures available for study and follow-up over long periods, or, where such populations exist, like Vietnam veterans and the Vietnamese, these have not been adequately studied. Thus, it is not surprising that, as reported below, only eight categories of adverse health effects have been found by the Task Force to have a "significant statistical association" (as defined by the VA) with exposure to phenoxyacetic acid herbicides and/or their associated contaminants even though many other adverse health effects have been shown to be associated with exposure.

The Methodology Used by the Task Force

The Task Force limited its review to epidemiologic studies of exposed humans, excluding experimental animal studies, because the VA's Advisory Committee has apparently not reviewed experimental animal studies. However, there is an overwhelming scientific consensus that carcinogenicity data derived from well-designed animal studies can be extrapolated with confidence to predict human cancer risk. Illustrative statements in the scientific literature of extrapolation of experimental carcinogenicity data to human
cancer risk is included as appendix A. Such experimental data have been and are accepted by legislators, regulators and courts in determining exposure risks and in establishing causal relationships. The epidemiologic evidence from a wide range of studies of an association between dioxin exposure and cancers and other chronic diseases is clearly supported by an extensive body of experimental data.

Carcinogenicity tests have demonstrated that dioxin is a potent chemical carcinogen which induces a wide range of cancers in a wide range of organs in a wide range of rodent strains and species. In fact, dioxin is the most potent carcinogen ever evaluated by the Carcinogen Assessment Group of the Environmental Protection Agency; dioxin is some four orders of magnitude more potent than the well-recognized highly carcinogenic dimethylnitrosamine. Such data establish a strong basis for the validity of a causal relation between exposure to Agent Orange and the subsequent development of a range of cancers.

Finally, there is a critical difference between the methodology used by the Task Force and that used by the VA's Advisory Committee. In its review of literature on non-Hodgkin's lymphoma, the Advisory Committee simply classified studies as positive or negative and then tallied them, apparently under the theory that all studies are equal and can be viewed independently from all other knowledge on the subject. This procedure is unprecedented and was not followed by the Task Force. Individual studies show associations in varying degrees, but the ultimate
conclusion about an association is the result of synthesizing all of the available data to determine their overall or aggregate meaning. The aggregate of all of the evidence derived from the available relevant epidemiologic studies establishes a causal relationship between Agent Orange exposure and a range of cancers and chronic diseases.

**Primary Conclusions of the Task Force**

Following review of the scientific literature, it is concluded there is a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and the following diseases: non-Hodgkin's lymphoma, soft tissue sarcoma, skin disorders/chloracne, subclinical hepatotoxic effects (including secondary coproporphyrinuria and chronic hepatic porphyria), and porphyria cutanea tarda (most likely only in individuals with inherited uroporphyrinogen decarboxylase deficiency). The aggregate interpretation of several sound studies showing a statistically significant association for each of these conditions makes this conclusion inescapable.

Further, the scientific evidence supporting the existence of a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) is at least as strong as the scientific evidence of a lack of the association for the following adverse health effects: Hodgkin's disease, neurologic effects, and
reproductive and developmental effects. For each of these health effects, there are sound scientific studies showing statistical significance and strong scientific evidence of an association between exposure and effect. However, a statistically significant association is not as consistently supported for these effects as for the first group of health effects.

There are other adverse health effects for which there is sound scientific evidence of an association with exposure, but the evidence does not reach the level of formal statistical significance. Nevertheless, were this Task Force a policy-making body concerned with disability compensation for veterans, it might conclude that compensation was due. However, the Task Force is limited to determining the existence of a significant statistical association, and the limited data available at this time show an association, but not a significant statistical association, between exposure to phenoxyacetic acid herbicides and/or dioxin and the following diseases: leukemias, cancers of the kidney, testis,

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2 The Task Force is informed that the law requires that the benefit of the doubt be given to veterans in determining whether an association between exposure and disease exists. See 38 U.S.C. § 354 note section 5(b)(2)(A)(i); Nehmer v. United States Veterans Administration, 712 F.Supp. 1404, 1420-1422 (N.D.Cal. 1989); 38 C.F.R. § 1.17; 54 Fed. Reg. 40389 (October 2, 1989). The VA has apparently defined this requirement to mean that, for disability compensation purposes, a statistically significant association will be deemed to exist if the evidence for and against the association is at least equally balanced, i.e., the association is "at least as likely as not." 38 C.F.R. § 1.17(d)(1). Because the Task Force found, for these three health effects, that the scientific evidence of a significant statistical association is at least as strong as the evidence of a lack of the association, these three health effects qualify under the VA's "at least as likely as not" test.
pancreas, stomach, prostate, colon, hepatobiliary tract, and brain, psychosocial effects, immunological abnormalities, gastrointestinal ulcer, and altered lipid metabolism. Further research should be directed at these associations, and policy-makers, cognizant of the limitations on finding significant statistical associations and of the obligation to give the veteran the benefit of the doubt, would be justified in viewing these disorders in a more conclusive light for the purpose of establishing entitlement to disability compensation.

Finally, the epidemiologic evidence on the associations between exposure and the adverse health effects described above is strongly supported by a wide range of experimental animal studies (EPA, 1985).

Evidence in support of the above conclusions is found in the summary statements which follow.

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CANCER

Following review of the scientific literature, it is concluded there is a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and non-Hodgkin’s lymphoma and soft tissue sarcoma, and that the evidence supporting the existence of such an association is at least as strong as the evidence of a lack of the association for Hodgkin’s disease. Evidence in support of these conclusions follows.

Non-Hodgkin’s Lymphoma

The veterans who served in the Marine Corps in Vietnam were seen to have a statistically significant (P <0.025) excess of non-Hodgkin’s lymphoma when compared with Marines who did not serve in Vietnam (Breslin, et al. 1987; 1988). Non-Hodgkin’s lymphoma has been associated with exposure to phenoxy herbicides (Hardell, et al. 1981; Hoar, et al. 1986) and arsenicals (Axelson, et al. 1978). The men who served in Vietnam had the potential for exposure to these agents. Agent Orange and Agent Blue, herbicides used in Vietnam, contained phenoxy herbicides and an organic arsenical, respectively. Several additional studies support the association between exposure to phenoxy herbicides and/or their associated contaminants (TCDD) and increase risk of non-Hodgkin’s lymphoma. A significantly increased risk of localized skin lymphoma was associated with phenoxy herbicide exposure (Olsson and Brandt, 1988), confirming results from an earlier case report (Olsson and Brandt, 1981). A significantly increased risk of non-Hodgkin’s

The Advisory Committee on Environmental Hazards of the Department of Veterans Affairs did not review the following studies (cited above) at its meeting of November, 1989, which considered non-Hodgkin's lymphoma: Breslin, et al. (1988); Axelson, et al. (1978); Olsson and Brandt (1988); Woods, et al. (1989); Burmeister, et al. (1983); Cantor (1982); Giles, et al. (1984); Buesching and Wollstadt (1984); Blair, et al. (1985); Bond, et al. (1989); Wiklund, et al. (1989); Ott, et al. (1987); Bishop and Jones (1981).

Further, with the studies it did review, the Advisory
Committee used a simplistic tallying system, wherein positive studies were somehow counterbalanced by studies classified as negative, with apparently no regard for the holistic, multidisciplinary approach that is standard practice in health assessment for regulatory and compensatory purposes. See National Academy of Sciences, Principles for Evaluating Chemicals in the Environment (1975). The need for such an approach has recently been reiterated by the National Academy of Sciences in its deliberations on the methods for the in vivo testing of complex mixtures (NRC 1988).

One of the studies called negative by the Advisory Committee was the Monsanto Company study of workers in its Nitro, West Virginia plant. This study has been relied upon in risk estimates of the human effects of dioxin exposure, but it has recently been challenged on the ground that exposed workers were improperly classified as non-exposed. This would produce a biased estimate of the risk of cancer and other diseases in these workers; the magnitude of the bias may be such that in the original study by Zack and Gaffey, which reported nine exposed workers with cancer and a relative risk of less than 1 compared to the U.S. reference population, should have reported eighteen exposed workers with cancer and a relative risk as high as 2.2. The EPA has apparently called for a reassessment of the Monsanto data with the goal of correcting the erroneous estimate of the risk of cancer by properly
classifying the exposure status of the decedents. Until this is done, this study should not be relied upon and any positions which relied upon the original results should be reconsidered.

The CDC Selected Cancers Study, released in April, 1990, found that veterans who served in Vietnam had a significantly increased risk of non-Hodgkin’s lymphoma over veterans who served elsewhere during the same period. This study may actually add support to the evidence that exposures in Vietnam caused increased risk of non-Hodgkin’s lymphoma, even though the authors deny that their data support the contention that Agent Orange was the cause. Although the study did not focus on any direct measure of Agent Orange exposure, and the proposed blood sampling to determine dioxin levels in patients was never carried out, the authors made conclusions concerning Agent Orange exposure.

First, the authors contend that Vietnam veterans who served in III Corps were most likely to be exposed to Agent Orange, and the results of their study indicate that they were at decreased risk of non-Hodgkin’s lymphoma. Second, the CDC study found excessive risk of non-Hodgkin’s lymphoma in "blue-water" Navy veterans whom the authors presume had no exposure to Agent Orange. Finally, the authors state that the responses to questions about spraying, handling or being around Agent Orange were similar among

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See Cate Jenkins, Characterization and Assessment Division, EPA, "Memo to Raymond Loehr [Chairperson of the Executive Committee of the Science Advisory Board, EPA]: Newly Revealed Fraud by Monsanto in an Epidemiological Study Used by EPA to Assess Human Health Effects from Dioxins," dated February 23, 1990.

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veterans with non-Hodgkin's lymphoma and veterans with no cancer of any type.

Critics have challenged these CDC interpretations of the data because the study did not contain any direct measure of exposure to Agent Orange. In addition, some indirect exposure criteria not emphasized by CDC do lead to the conclusion of adverse health effects in exposed veterans. For example, one of the heavily sprayed regions in Vietnam was I Corps. If the CDC data on veterans in I Corps and III Corps are taken together, they show an increased risk of both non-Hodgkin's lymphoma and soft tissue sarcoma. These two cancers have been found elevated in other studies of veterans done by state health departments in Massachusetts, West Virginia and Wisconsin. At a minimum, the CDC findings should be put in the context of these other studies of veterans, as well as studies of agricultural workers exposed to herbicides. It is impossible, without access to CDC's complete data, to conclusively determine whether Agent Orange played a part in the increased risk reported in the study.

A hearing on the Selected Cancers Study before the House Veterans Affairs Committee was conducted on April 4, 1990. It is reported that CDC's Dr. William Roper, although acknowledging that the Selected Cancers Study was not a dioxin study, repeatedly pointed to the Air Force's Ranch Hand study as a dioxin study with good exposure data that showed no increased cancer risk. However, in the February, 1990 release of the "1987 Follow-up Examination Results" on Ranch Hand, it is stated that the exposure index used
in the data analysis "is not a good measure of actual dioxin exposure," and it is also stated that statistically significant individual findings are not possible because of the size of the group under study. Furthermore, in this release, statistically significant group differences with a harmful impact on Ranch Hand veterans were detected in several health areas, including all cancers combined, both verified and suspected, and skin cancers alone.  

Regarding CDC studies and Agent Orange exposure, the CDC cancelled its study of Vietnam veterans exposed to Agent Orange, claiming it was not possible to determine exposure to Agent Orange from military records. CDC instead conducted an Agent Orange validation study which concluded there was no correlation between exposure, as predicted by certain military records, and dioxin levels in tissue and serum samples of certain veterans. CDC’s conclusions in cancelling the Agent Orange exposure study and its conclusions in the validation study were the subject of a Congressional hearing on July 11, 1989. At the hearing, scientists who worked on or were associated with the projects testified and submitted statements criticizing the studies and the conclusions,

4 The 1990 Ranch Hand release also showed statistically significant group differences, with a harmful impact on Ranch Hand veterans, in the following additional health areas: hereditary and degenerative neurological diseases; coordination abnormalities; psychological and sleep disorders; certain dermatologic disorders; pulse irregularities; increase in thyroid stimulating hormone; among black Ranch Hands, higher mean counts for "natural killer cells" as compared to blacks in the control group; and among Ranch Hands who are heavy smokers, more abnormal composite skin reactions as compared to heavy smokers in the control group.
and they can no longer be taken at face value. See Oversight Review of CDC's Agent Orange Study, Hearing before the Human Resources and Intergovernmental Relations Subcommittee of the Committee on Government Operations, House of Representatives (101st Congress, First Session, July 11, 1989).

**Soft Tissue Sarcoma (STS)**

Kogan and Clapp (1988) reported that STS mortality was significantly elevated among Vietnam veterans in Massachusetts from 1972 - 1983. In a follow-up study, Clapp (1988) found that STS mortality was still significantly elevated among Vietnam veterans in Massachusetts from 1982 - 1988. Studies of West Virginia and Wisconsin veterans also reported that STS mortality was significantly elevated among veterans who served in Vietnam (Holmes, et al. 1986; Anderson, et al., 1986). In a case-control study, Kang, et al. (1987) reported a greater risk of STS (odds ratio of 8.64) in a subgroup of Vietnam veterans who served in an area where Agent Orange spraying was reported to be extensive and thus who had higher opportunities for exposure to Agent Orange. However, this risk was not statistically significant based in part on the weak study power of the subgroup comparison.

An association between STS and occupational exposure to phenoxyacetic acid herbicides and/or their associated contaminants (TCDD) has been reported in a number of studies. Case-control studies from Sweden reported a statistically significant increased risk of STS in workers exposed to phenoxyacetic acids, chlorophenols, and their associated contaminants including
chlorinated dioxins (Hardell and Sandstrom, 1979; Eriksson, et al., 1981). The publication of these initial studies was followed by several case reports from the United States of STS associated with exposure to these chemicals (Moses and Selikoff, 1981; Honchar and Halperin, 1981; Cook, 1981; Johnson, et al., 1981). More recently, 4 new studies reported a statistically significant increased risk of STS in workers exposed to phenoxyacetic acids and/or their associated contaminants, including chlorinated dioxins (Lynge, 1985; Vineis, et al., 1986; Hardell and Eriksson, 1988; Bond, et al., 1989). The most recent report of Bond, et al., (1989) was an update on a cohort of 2192 employees potentially exposed to chlorinated dioxins, including TCDD. Cancer deaths were analyzed in a subset of 323 men in which exposure was confirmed by the presence of chloracne. In men with chloracne, only STS displayed a statistically significant increase over the expected levels (2 observed; <0.1 expected).

A recent study (JNCI, 1990) by Eriksson, Hardell and Adami re-evaluated the association between exposure to TCDD and other chlorinated isomers of dioxin and the risk of soft tissue sarcoma. This study was based on 237 cases from a Regional Cancer Registry in central Sweden and it confirmed findings from the earlier studies in northern Sweden. The authors conclude that the study supports previous findings of increased risk of soft tissue sarcoma in patients exposed to phenoxyacetic acids or chlorophenols, and furthermore that 2,3,7,8-TCDD and other chlorinated isomers may be the specific risk factor for this cancer.

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Environmental and human exposure to TCDD occurred in 1976, following an accidental explosion in a plant near Seveso, Italy. In 1986, a report of cancer-specific incidence rates for the Seveso population found only STS at a higher incidence in the exposed than in the unexposed group (Puntoni, et al., 1986). In a ten-year mortality study of the population involved in the Seveso incident, although not statistically significant, Bertazzi, et al., (1989) reported elevated relative risks of STS of 24 and 6.33 in two subgroups of this population.

Hodgkin's Disease

Among cancer deaths, there was strong statistical evidence to suggest that Hodgkin's disease was more common among West Virginia veterans who served in Vietnam than among veterans who did not (Holmes, et al., 1986). Wikland, et al., (1988) reported a significant increase in the relative risk of Hodgkin's disease in men engaged in silviculture who were exposed to phenoxy acid herbicides. A time-related rising trend in the relative risk of Hodgkin's disease was also found in the silviculture cohort. In another study of 20,245 Swedish pesticide applicators who had exposure to phenoxy acid herbicides, Wiklund, et al. (1989) reported a statistically significant increased risk of Hodgkin's disease in the licensed pesticide applicators. A significantly elevated proportionate mortality ratio for Hodgkin's disease was also reported in a study of agricultural extension agents in the cooperative extension service of the USDA (Alavanja, et al., 1988). And an increased mortality rate for Hodgkin's disease was also
reported in a ten-year mortality study of the population involved in the Seveso incident in 1976 (Bertazzi, et al., 1989).

**Other Cancers**


The limited data available at this time do not permit a conclusion of a formal statistically significant association between exposure to phenoxyacetic acid herbicides and/or dioxin and these diseases. Further research should be directed at these associations.

It should be noted that one reason why studies are finding cancers at diverse sites may be that dioxin is a potent promoter and may well interact with other coexposures such that tumors may be induced at many sites depending upon these interactions (e.g., the initiator exposure may determine site, the promoter may then determine actual expression).
SKIN CONDITIONS/CHLORACNE

Following review of the scientific literature, it is concluded there is a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and skin conditions/chloracne. Evidence in support of this conclusion follows.

American Legionnaires who served during the Vietnam war were studied via a mailed questionnaire. Agent Orange exposure was significantly dosage-related to history of adult acne, skin rash with blisters and change of skin color (Stellman, et al., 1988). Several other studies have confirmed that Chloracne is associated with human exposure to TCDD (Taylor, 1974; MMWR, 1988; Suskin, 1985; Caputo, et al, 1988; Tindall, 1985; Del Corno, et al., 1985; Moses and Prioleau, 1985).

However, it is important to note that recent studies in the Seveso population have found no threshold level for expression of chloracne (MMWR, 1988). Serum TCDD levels (on a lipid weight basis) range from 828 to 27,821 ppt in individuals with chloracne and 1,772 to 10,439 ppt in individuals with no chloracne. Thus, there is great variability in individual responses in TCDD exposure and chloracne may not be a reliable single marker of exposure (Del Corno and Montesarchio, 1985). This means that although chloracne may be taken as indicative of exposure to dioxin or to a dioxin-like compound, the absence of chloracne does not, by itself, necessarily imply a lack of exposure.
SUBCLINICAL HEPATOTOXIC EFFECTS

Following review of the scientific literature, it is concluded there is a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and subclinical hepatotoxic effects. Evidence in support of this conclusion follows.

Subclinical hepatotoxic effects, including elevated serum liver enzymes and elevated urine coproporphyrin, have been reported in Ranch Hand personnel who were responsible for herbicide spraying in Vietnam (Albanese, 1988). The CDC Vietnam Experience Study (II Physical Health, 1988) also found Vietnam veterans to have statistically elevated levels of the serum liver enzyme, gamma-glutamyl transferase. Studies of residents of Quail Run mobil home park in Missouri also suggest subclinical hepatotoxic effects associated with long-term low level exposure to TCDD (Hoffman, et al., 1986; Knutsen, et al., 1987; Stehr-Green, et al., 1987, 1988). Elevated serum liver enzymes have been reported in children exposed to dioxin in Seveso, Italy (Mocarelli, et al., 1986). All of the above findings are supported by studies of industrial workers which reported subclinical liver injury associated with dioxin exposure (Moses, et al., 1984; May, 1982; Pazderova-Vecjulpkova, et al., 1981).

PORPHYRINOPATHY

Following review of the scientific literature, it is concluded
there is a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and porphyria cutanea tarda (most likely only in individuals with inherited uroporphyrinogen decarboxylase deficiency). Evidence in support of this conclusion follows.

In the CDC Vietnam Experience Study (II Physical Health, 1988), one Vietnam veteran had a clearly abnormal pattern of urinary porphyrin levels (none in the non-Vietnam group).

Recently, Doss (1987) concluded that individuals exposed to TCDD can develop a secondary coproporphyrinuria with transition to latent chronic hepatic porphyria as a toxic hepatic response, and probably do not suffer from the clinical stage of porphyria cutanea tarda unless a hereditary disposition exists. In other words, TCDD induces an incipient subclinical stage of chronic hepatic porphyria in persons with normal red cell uroporphyrinogen decarboxylase. In contrast, exposure to dioxin in persons with inherited uroporphyrinogen decarboxylase deficiency can cause latent chronic hepatic porphyria to develop into porphyria cutanea tarda. Coproporphyrinuria and latent chronic hepatic porphyria do not produce clinical symptoms. Secondary porphyrinuria with transition to chronic hepatic porphyria is a metabolic response following various toxic and pathologic conditions; it serves as a sensitive index for chemical exposure and occupational disease. The conclusions of Doss (1987) are also supported by Strik (1987), Doss and Colombi (1986), and Doss, et al. (1984).

There are several older cases of occupational exposure to TCDD

**NEUROLOGIC EFFECTS**

Following review of the scientific literature, it is concluded that the evidence supporting the existence of a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and neurologic effects, both central and peripheral, is at least as strong as the evidence of a lack of the association. Evidence in support of this conclusion follows.

In the baseline Ranch Hand morbidity study (Lathrop, et al., 1984), an extensive battery of neurologic function tests showed an increased incidence of abnormal Babinski reflexes in Ranch Hand personnel compared to the comparison group and an exposure-related decrease in nerve conduction velocity of the ulnar nerve only in enlisted flyers. The authors dismissed these effects because they did not find defined neurologic disease in the cohort. The same measures of neurologic health and function (except for nerve conduction velocity) were evaluated in the follow-up morbidity study of Ranch Hand personnel (Lathrop, et al., 1987) as in the baseline study. The results of this analysis were similar to those of the baseline study. Overall, the number of abnormalities decreased in both the Ranch Hand and the comparison group during the interval between the studies. The difference between the
groups with regard to Babinski reflex seen in the baseline study was not seen in the follow-up. In fact, the Ranch Hand cohort had fewer abnormal Babinski reflexes than the comparison group in this study. While there were no statistically significant differences between the Ranch Hand cohort and the comparison group in any of the 27 measures of neurologic function in the follow-up study, abnormalities in some of these measures tended to cluster in the Ranch Hand cohort. The authors concluded, therefore, that continued surveillance of neurologic function was necessary within the cohort. Finally, as stated earlier, in the February, 1990 release of the "1987 Follow-up Examination Results" on Ranch Hand, statistically significant group differences with a harmful impact on Ranch Hand veterans were detected in several health areas, including, hereditary and degenerative neurological diseases.

The recent CDC Vietnam Experience Study (II Physical Health, 1988) reported that Vietnam veterans had a higher incident (3.0%) of symptoms of peripheral neuropathy (numbness, tingling, burning sensation, or weakness of arms or legs) than non-Vietnam veterans (1.9%). However, this difference was not statistically significant.

Klawans (1987) and Klawans, et al. (1987) reported neurologic problems in 47 railroad workers who were exposed to polychlorinated phenols contaminated by dioxin in early 1979 while cleaning up the chemical spillage following damage to a tank car filled with these chemicals. The initial neurological complaints included a sense of fatigue and muscle aching, both of which have been reported in
other individuals following dioxin exposure (Holmstedt, 1980; Oliver, 1975; Bogen, 1979; Pazderova-Vejlupkova, et al., 1981). On detailed neurological examination in December, 1985, 24 of 45 workers (2 had committed suicide) had dystonic writer's cramp and/or action dystonias of the hands. None of the involved individuals had a family history of the dystonia, and all 24 dated the onset of the dystonia to the first 2 to 3 years subsequent to early 1979. Thirty-five of the 45 workers also manifested postural and terminal intention tremor which resembled benign essential tremor. None of the involved individuals had a family history of tremor and all dated the onset of the tremor after early 1979. Forty-three of the 45 patients had histories and findings suggestive of peripheral neuropathy. In summary, Klawans (1987) and Klawans, et al., (1987) reported a rather stereotyped set of neurologic problems following exposure to TCDD. This syndrome initially included fatigue, muscle cramping and peripheral neuropathy followed by depression, changes in mentation and finally by action dystonias and tremors on the hands.

Peripheral neuropathy following accidental exposure to TCDD has also been reported by other investigators. Subclinical neurologic damage, including reduced nerve conduction velocity, was reported at a greater incidence in residents of Seveso, Italy, who were exposed to TCDD (Pocchiari, et al., 1979). Barbieri, et al. (1988) recently reported that clinical and electrophysiologic signs of peripheral nervous system involvement occurred with a statistically increased frequency in the Seveso population 6 years
after the accident, although a peripheral neuropathy was not evident in any of the chloracne patients using the WHO diagnostic criteria. In a 10-year study of 80 workers exposed to TCDD between 1965 and 1968, Pazderova-Vejlupkova, et al. (1981), reported that 23% of the exposed workers had peripheral neuropathy predominantly involving the lower extremities. Singer, et al. (1982) also performed nerve conduction velocity studies in workers employed in the manufacture of phenoxy herbicides. Duration of employment was significantly correlated with slowing of sural nerve conduction velocity. Altogether, 46% of the study group had one or more slowed nerve conduction velocities, versus 5% of the control group (P<0.001).

Goldstein, et al. (1959) reported that humans exposed to 2,4-D have neurologic symptoms which include numbness in the fingers and toes, muscle aches and fatigue, and tetany of the limb muscles and ataxia. 2,4-D has been reported to inhibit normal nerve functioning, decreasing nerve conduction velocities and damaging peripheral nerves. These effects have been described as peripheral neuropathy (Wallis, et al., 1970). The neuromuscular syndrome in humans associated with 2,4-D exposure thus consists of hyperesthesia and myotonia in the muscles of the extremities, hyporeflexia, and general muscular weakness leading to ataxia. Central nervous system effects have also been reported and were manifested as aberrant spontaneous electrical activity of the cerebral cortex and reticular formation as measured by EEG (Kontek, et al., 1973).
REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Following review of the scientific literature, it is concluded that the evidence supporting the existence of a significant statistical association between exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) and reproductive and developmental effects is at least as strong as the evidence of a lack of the association. Evidence in support of this conclusion follows.

Fertility

The CDC Vietnam Experience Study (1988) found Vietnam veterans to have significantly lower mean sperm concentration and significantly lower levels of morphologically "normal" sperm than non-Vietnam veterans. Both of these parameters have traditionally been used as indicators of reduced fertility potential.

Miscarriage

The percentage of spouses' pregnancies which resulted in miscarriages was significantly higher for Vietnam veterans than controls. Logistic regression analysis showed that Agent Orange exposure and maternal smoking were both independently and significantly associated with miscarriage rates in a dose-related manner (Stellman, et al., 1989). A statistically significant association between increasing herbicide exposure and miscarriage was also reported in the officer subgroup in the Air Force Study of Ranch Hand personnel who were responsible for herbicide spraying in Vietnam (Albanese, 1988). Greater fetal loss was also reported
in a population of Vietnam veterans currently living in Tasmania (Field and Kerr, 1988). Accidental exposure to TCDD in 1976 in Seveso, Italy, has also been associated with an apparent elevation in the rate of spontaneous abortions in the exposed population (Bruzzi, 1983; Bianco, et al., 1984).

Of all the Vietnamese studies, the North Vietnamese studies by Nguyen Can, et al. (1983) and Ton Duc Lang, et al. (1983, 1986) appear to have been conducted most nearly in accordance with accepted epidemiologic methods. They both support the hypothesis that paternal exposure to the components of Agent Orange (while serving in South Vietnam) can adversely affect the products of conceptions occurring considerably later (post-war North Vietnam). Nguyen Can, et al. (1983) reported that elevated incidences of spontaneous abortion and congenital malformation, but not stillbirth or molar pregnancy, were associated with the father having been in South Vietnam during the war. Ton Duc Lang, et al. (1983, 1986) also claimed that the degree of the father's exposure, determined by the region of South Vietnam in which they had served, was associated with the extent to which the incidence of malformations was increased.

Birth Defects

Several studies report a higher incidence of selected birth defects in children of Vietnam veterans than controls. An Air Force study of Ranch Hand personnel, responsible for the herbicide spraying in Vietnam, reported a statistically significant increase in reported birth defects in the Ranch Hand group (Albanese, 1988).
Defects reported in the Ranch Hand group included skin defects, neural tube defects, heart defects, oral clefts, and kidney defects. A preliminary analysis of medical records of children reported abnormal has also indicated that overreporting of defects may not account for the excess in birth defects in the Ranch Hand group. A recent CDC study (CDC, 1988) reported that hospital birth records did show a higher incidence of live births with cerebrospinal malformations in children of Vietnam veterans, however the results were not statistically evaluated. Erickson, et al. (1984) also reported that the risks for fathering an infant with spinabifida, cleft lip (with or without cleft palate), and "other neoplasms" such as neuroblastomas were higher for Vietnam veterans than controls. These increases were also significantly associated with increased scores on the Agent Orange Exposure Opportunity Index (Erickson, et al., 1984). An increased incidence of birth defects was also reported in a population of Vietnam veterans currently living in Tasmania (Field and Kerr, 1988). The veteran's reproductive outcome contained significantly more children with major and minor abnormalities, tumors, chronic health problems, and learning, behavioral, sensory and other relatively minor problems. Field and Kerr (1988) found three tissue systems were predominantly affected: the central nervous, the skeletal, and cardiovascular systems. Reproductive studies in North Vietnamese populations also report an association between paternal exposure to Agent Orange, while serving in South Vietnam, and an elevated incidence of congenital malformation (Nguyen Can, et al.,
Additional reports of reproductive studies of populations potentially exposed to dioxins in Seveso, Italy, and in Midland County Michigan suggest the possibility of increased incidences of birth defects. A suggestive increase in the rates of certain birth defects (angioma, CNS defects, hypospadias, hip dislocation, defects of the digestive tract) has been reported in the Seveso population potentially exposed to dioxin (Bruzzi, 1983; Bianco, et al., 1984). The Michigan Dept. of Public Health (MDPH, 1983) examined the rates of birth defects in Midland County and for the period from 1970 to 1975 reported significantly elevated rates of hip dislocations, cleft lip with or without cleft palate, cleft palate without cleft lip, hypospadias, and epispadias relative to the rate in the state as a whole. In a subsequent investigation of the potential association between exposure to trichlorophenol and its associated chlorinated dioxin contaminants and birth defects, Lock, et al. (1984) investigated birth outcomes in 29 trichlorophenol-producing counties in the United States. The rates of hip dislocation without CNS involvement and atrial septal defects were significantly elevated in 6 to 29 trichlorophenol-producing counties.

In summary, elevated incidences of specific birth defects have been found in several studies. Elevated rates of hypospadias, oral clefts, cardiovascular defects, and hip dislocations have been reported in more than one study and are thus suggestive of an association between these defects and exposure to phenoxy
herbicides, chlorophenols and their associate chlorinated dioxin contaminants. Definitive interpretation of the assembled data on the reproductive toxicity of these substances in humans is constrained by limited power of the studies to detect modest increase in detrimental effects, inadequate characterization of actual exposure, and possible biases in reporting of adverse effects.

OTHER HEALTH EFFECTS

Other health effects which are associated, but not with formal statistical significance, with exposure to phenoxyacetic acid herbicides and/or their associated contaminants (chlorinated dioxins) are described below.

Immunological Abnormalities

Jennings, et al. (1988) investigated immunological abnormalities 17 years after accidental exposure to TCDD. Antinuclear antibodies and immune complexes were detected significantly more frequently in the peripheral blood of workers exposed to dioxin. Although the significance of this finding is not clear, it may reflect prior tissue damage and cellular destruction in the exposed population. The number of natural killer cells identified by the monoclonal antibody Leu-7 was significantly higher in workers exposed to dioxin. Natural killer cells are believed to contribute to defense against viruses and tumors. If exposure to dioxin is associated with an increased risk of neoplastic disease, the number and function of natural killer
(NK) cells may be important in its pathogenesis. Alternatively, changes in the number of NK cells may show activation of the body's defenses. The authors suggest that further studies of NK cell number and function should be conducted in subjects exposed to dioxin.

Studies of residents of Quail Run mobile home park in Missouri suggest alterations in immune function, but these were not consistently found (Hoffman, et al., 1986; Knutsen, et al., 1987; Stehr-Green, et al., 1987, 1988). Immunologic tests showed that the exposed group had an increased frequency of anergy (11.8% vs. 1.1%) and relative anergy (35.4% vs. 11.8%); the exposed group also had non-statistically significant increased frequency of abnormal T-cell subset tests (10.4% vs. 6.8%), a T4/T8 ratio < 1.0 (8.1% vs. 6.4%) and an abnormality in the \textit{in vitro} functional T-cell tests (12.6% vs. 8.5%). The authors concluded that these findings suggest an association between long-term exposure to TCDD and depressed cell-mediated immunity, although the effects have not resulted in an excess of clinical illness in the exposed group.

Immune function was evaluated between 1976 and 1979 in 48 children from Seveso who were heavily exposed to TCDD (Mocarelli, et al., 1985). Exposed children showed higher titers of total hemolytic complement activity than controls in all the screens. They also had lymphocyte responses to phytohemagglutinin and poke weed mitogen significantly higher than controls in the first half of the screens.

\textbf{Gastrointestinal Tract Ulcer}
Two studies of workers exposed to 2,4,5-T and TCDD have reported a statistically significant greater frequency of gastrointestinal ulcer in the exposed populations (Bond, et al., 1983; Suskind and Hertzberg, 1984). The CDC Vietnam Experience Study (II Physical Health, 1988) reported that occult blood was found in the stool samples of more Vietnam (1.3%) than non-Vietnam (0.5%) veterans. While this finding is suggestive of injury to the gastrointestinal tract, there was no report of a greater frequency of ulcer in the population of Vietnam veterans.

**Psychosocial Effects**

A CDC Vietnam Experience Study (1988) reported that 15 to 20 years afterward, more Vietnam veterans have psychological and emotional problems compared with veterans who did not serve in Vietnam. Psychological problems significantly more prevalent among Vietnam veterans include depression (4.5% of Vietnam veterans vs 2.3% of non-Vietnam veterans), anxiety (4.9% vs 3.2%), and alcohol abuse or dependence (13.7% vs 9.2%). About 15% of Vietnam veterans experienced combat-related post-traumatic stress disorder at some time during or after military service, and 2.2% had the disorder during the month before the examination.

Through use of a battery of neuropsychological tests, Levy (1988) reported evidence of organic psychological deficits in Vietnam veterans exposed to Agent Orange. The exposed group consisted of 6 individuals with active cases of Chloracne, a medical indication of exposure to Agent Orange. The 25 control subjects also served in Vietnam, may have been exposed to Agent
Orange, but apparently never showed signs of chloracne. It is important to note that there is a large interindividual variability in the expression of chloracne and no apparent threshold of exposure necessary for this response. The exposed Vietnam veterans showed a significantly higher rate of post-traumatic stress disorder and its associated features of depression, anxiety, and increased aggression. Levy suggests that for certain individuals this condition cannot be explained by combat stress alone and that Agent Orange exposure may contribute to this disorder. Industrial workers who have been exposed to TCDD present psychological symptoms (Bauer, et al., 1961; Oliver, 1975) which duplicate those that have been attributed to the delayed effects of combat stress in Vietnam veterans.

Stellman, et al., (1988) investigated the social and behavioral consequences of the Vietnam experience among American Legionnaires. They reported that men who faced high levels of combat intensity were found to be at greater risk for divorce and for generally being less happy and satisfied with their lives, their marriages, their role as fathers, and as sexual human beings. Their data also gave some indication that certain behavioral effects related to combat intensity may be exacerbated by concurrent exposure to herbicides and indicate the need for further exploration of this issue. In a related study, Snow, et al., (1988) found a distinct linear dose-response relationship between combat stress and a quantitative measure of post-traumatic stress disorder intensity. The potential contributing role of Agent
Orange exposure was not considered in this study.

Poland (1971) found high scores for hypomania on the Minnesota Multiphasic Personality Inventory to be associated with chloracne and 2,4-D and 2,4,5-T exposure. Oliver (1975) reported personality changes in a small number of laboratory workers exposed to TCDD.

Green (1987) reported a statistically significant excess number of deaths due to suicide in a group of 1,222 male forestry workers who were exposed to 2,4-D and 2,4,5-T. Fitzgerald, et al. (1989) reported on health effects 3 years after potential exposure to the toxic contaminants of an electrical transformer fire (potential exposure to PCBs, PCDFs and PCDDs). Two suicides were observed compared with 0.31 expected, but the difference was not statistically significant, (482 persons were potentially exposed).

**Altered Lipid Metabolism**

There is a relatively consistent finding in many populations of altered lipid metabolism, expressed as altered HDL/LDL, cholesterol, and triglyceride levels, which is consistent with what is known about the metabolic effects of dioxin in animal studies. This has implications for the potential risk of cardiovascular disease (Silbergeld and Gasiewicz, 1989).

**HUMAN EXPOSURE TO 2,3,7,8-TCDD**

**2,3,7,8-TCDD in Human Adipose Tissue**

In human adipose tissue, levels of 2,3,7,8-TCDD averaging 5-10 ppt have been reported for background populations in St. Louis, MO, by Graham, et al. (1986), in Atlanta, GA, and Utah by
Patterson, et al. (1986), and in Canada by Ryan, et al. (1985). Sielken (1987) evaluated these data and concluded that the levels of 2,3,7,8-TCDD in human adipose tissue are log-normally distributed and positively correlated with age. Among the observed United States background levels of 2,3,7,8-TCDD in human adipose tissue, more than 10% were >12 ppt.

Patterson, et al. (1986) analyzed the adipose tissue of 39 persons with a history of residential, recreational or occupational exposure in Missouri, and in 57 persons in a control group. All participants had detectable levels of 2,3,7,8-TCDD in their adipose tissue, but the exposed group had significantly higher levels. Levels in six of the exposed persons were more than 5 times greater than the level of the highest control. Thus, measuring 2,3,7,8-TCDD in adipose tissue can provide an index of exposure.

Adipose tissue has been examined to determine if levels of 2,3,7,8-TCDD in this reservoir correlated with exposure. Adipose tissues of Vietnam veterans exposed to Agent Orange and humans occupationally exposed to potential sources of 2,3,7,8-TCDD were reported to have up to 10 times the level of 2,3,7,8-TCDD than unexposed control subjects (Schecter, et al., 1985, 1987, 1989; Gross, et al., 1984, Kahn, et al., 1988); however, another study by Weerasinghe, et al. (1986) failed to detect any difference between a group of 13 veterans and unexposed subjects. In the most recent study, Schecter, et al., (1989) reported the highest adipose tissue levels of 2,3,7,8-TCDD in veterans who handled the Agent Orange herbicide.