Proposed Peripheral Neuropathy and Lung Cancer Regulations Published

On January 21, 1991, the Department of Veterans Affairs (VA) issued proposed regulations regarding claims for service-connected disability based on exposure to herbicides containing dioxin. These proposals deal specifically with peripheral neuropathy and lung cancer.

The proposed amendments are designed to implement Secretary of Veterans Affairs Edward J. Derwinski’s determination that (1) there is a significant statistical association between exposure to herbicides containing dioxin and the subsequent development of peripheral neuropathy, and (2) there is no significant statistical association between exposure to herbicides containing dioxin and lung cancer.

Peripheral Neuropathy Deemed Service-Connected Under Certain Circumstances

Under the proposal, VA would add peripheral neuropathy to the list of diseases for which service-connection may be granted on the basis of exposure to herbicides containing dioxin. Peripheral neuropathy is a nervous system condition that causes numbness and tingling and/or weakness.

The amendment stipulates that two requirements deriving from the application of sound scientific and medical principles be addressed in all adjudication decisions: (1) peripheral neuropathy must appear within 10 years of exposure, and (2) certain confounding factors must be ruled out as causes. The confounding factors include, but are not limited to, the effects of aging, alcohol abuse, trauma, diseases known to be associated with peripheral neuropathy (examples, diabetes, Guillain-Barre syndrome, etc.), and exposure to substances other than dioxin that are known to produce peripheral neuropathy.

The peripheral neuropathy decision was based on a recommendation of the Veterans’ Advisory Committee on Environmental Hazards. During its May 23, 1991 meeting, the Committee considered 11 valid studies that related to peripheral neuropathy and dioxin exposure. Three of these studies demonstrated positive findings relative to peripheral neuropathy. One study found a very high prevalence of peripheral neuropathy among study subjects who experienced a heavy exposure to dioxin, as measured by the presence of chloracne or raised serum hepatic enzyme levels.

Another study reported peripheral neuropathy among individuals exposed to polychlorinated phenols as a consequence of a tank car accident. The Ranch Hand study, which involved comparatively low exposure levels, presented mild evidence of a sustained neurologic effect.

After VA’s review of the studies and the Committee’s recommendation, the Secretary determined on June 27, 1991, that there is a significant statistical association between exposure to herbicides containing dioxin and peripheral neuropathy.

No Service-Connection for Lung Cancer

On May 23, 1991, the Advisory Committee also considered approximately 40 studies dealing with lung cancers. The Committee observed that most of these studies failed to deal adequately with documentation of exposure and potential confounding factors, particularly smoking. The Committee agreed that a study which did not adequately address smoking would be considered invalid. The only study to address the factor of smoking, the Ranch Hand study, was negative with regard to lung cancer.

The Committee concluded that, on the basis of available epidemiological data, there is no evidence of a significant statistical association between exposure to herbicides containing dioxin and lung cancer.

After VA reviewed the evidence and the Committee findings, the Secretary made his determination that sound scientific medical evidence does not establish an association between herbicides containing dioxin and lung cancer.

The proposed effective date of the adjudication amendments is September 25, 1985, which was the effective day of VA's original regulations governing claims based on exposure to herbicides containing dioxin. The original regulations were voided by a court ruling in 1989.

Under the proposal, peripheral neuropathy would join chloracne and soft tissue sarcomas as diseases associated with exposure to herbicides containing dioxin, and lung cancer would be added to porphyria cutanea tarda on the list of diseases without such an association. Non-Hodgkin’s lymphomas, which some scientists suspect may be related to exposure to herbicides containing dioxin, were recognized as service-connected by VA in 1990 for Vietnam veterans, but non-Hodgkin’s lymphomas were not associated in VA regulations to herbicide exposure.

The proposed regulations were published in the Federal Register for public comment on January 21, 1992. The deadline for public comments was February 20, 1992. After a careful review of all comments, suggestions, or objections regarding this proposal, VA will make any necessary changes and publish final regulations. It is anticipated that the regulations will be finalized later this year.
The NAS is due not later than July 31, 1993. Under the terms of the contract with VA, the first report by

the NAS will review and summarize scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used in Vietnam.

For each disease suspected of being associated with exposure to an herbicide, the NAS will review and summarize the relevant scientific evidence and determine (1) whether there is a statistical association with exposure to the herbicide; (2) the increased risk of disease among those exposed to the herbicides during service in Vietnam; and (3) whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The NAS also may make recommendations for further studies to resolve areas of continuing scientific uncertainty about the health effects of exposure to herbicide agents.

Under the term of the contract with VA, the first report by the NAS is due not later than July 31, 1993.

Impact on Other Provisions

The initial NAS report is to include recommendations as to whether programs described in sections 6-9 of Public Law 102-4 should be implemented. Any VA action on these sections will be based, to a large extent, on the recommendations in the NAS report.

The effective date of sections 6-9 is 90 days after receipt of the report unless VA determines that it is not feasible or cost-effective to carry out any or all of these programs or that implementation would not make a material contribution to the body of scientific knowledge concerning the health effects in humans of herbicide exposure. If such a determination is made, VA must notify the Senate and House Committees on Veterans’ Affairs. Implementation of each of these programs can begin only if Congress specifically makes funds available.

Section 6 requires the compilation and analysis of data from VA examinations and treatment.

Section 7 requires the establishment of an archiving system for blood and tissue samples contributed voluntarily by Vietnam veterans to facilitate scientific research on the effects of veterans’ exposure to dioxin and other agents in herbicides.

Section 8 requires VA to establish, in consultation with the NAS, a program of pilot studies of the feasibility of conducting additional scientific research on health hazards of exposure to herbicide agents or service in Vietnam.

Section 9 requires VA to test for dioxin (TCDD) in any blood sample voluntarily provided by Vietnam veterans who seek VA health care under priority eligibility based on exposure to Agent Orange.

The law also authorizes follow-up reviews by the NAS, to the extent that appropriations are available, at least once every two years for ten years after the initial report.

Section 3 of Public Law 102-4 directed VA to seek to enter into an agreement with the NAS on this project not later than two months after enactment of the legislation. The legislation indicated that if VA was unable to enter into an acceptable agreement during this period, VA should "seek to enter into an agreement for the purposes of this section with another appropriate scientific organization that is not part of the Government and operates as a not-for-profit entity and that has expertise and objectivity comparable to that of the National Academy of Sciences."

During extensive negotiations, NAS officials expressed concern about the Academy’s potential liability under such an agreement. Congress acted promptly to remedy this situation. Public Law 102-86, the "Veterans' Benefits Programs Improvement Act of 1991," passed by Congress in late July and signed by the President on August 14, 1991, amended section 3 of Public Law 102-4 to authorize VA to provide liability insurance for the NAS or any other contract scientific organization to cover "any claim for money damages for injury, loss of property, personal injury, or death caused by any negligent or wrongful act or omission of any person” in carrying out this section.

Public Law 102-86 also authorized additional time for VA to conclude an agreement with the NAS. With enactment of Public Law 102-86, the major impediment to the Academy’s acceptance of this project was removed, and NAS President Frank Press contacted Secretary Derwinski in November 1991 to indicate NAS willingness to undertake this project. Final details of the tentative agreement were determined in late January.

Women Vietnam Veterans Research Advances

Some observers have complained that because of the relatively small number of women who served in the Armed Forces in Vietnam, the health problems and concerns of these women have been ignored by scientists who have focused their research on the possible long-term health consequences of military service in Vietnam veterans and exposure to herbicides, including Agent Orange. However, significant steps have been undertaken by VA scientists to learn more about the problems that these women have suffered or may experience in the future.

The Mandate

Public Law 99-272 mandates an epidemiologic study of any long-term adverse health effects experienced by women who served in the U.S. Armed Forces in Vietnam. The law also requires that the proposed protocol be approved by the Congressional Office of Technology Assessment (OTA) before the study is conducted. After a series of reviews and revisions of the proposed study protocols, officials of the OTA, congressional committees, and VA concluded that the comprehensive health study of women Vietnam veterans as envisioned by Congress in Public Law 99-272 was not scientifically feasible.
In lieu of the comprehensive study, VA proposed three alternate research projects. These are (1) a study of post-service mortality among women Vietnam veterans; (2) an indepth analysis of post-traumatic stress disorder (PTSD) and other psychological health outcome data already collected for women Vietnam veterans in the National Vietnam Veterans Readjustment Study (NVVRS); and (3) a study of reproductive outcomes among women Vietnam veterans.

**Women Vietnam Veterans Mortality Study**  
**Results Published**

The Women Vietnam Veterans Mortality Study was completed and the results were published in the *American Journal of Epidemiology* in November 1991. VA investigators found that women Vietnam veterans had lower than expected mortality from all causes compared to U.S. women and women non-Vietnam veterans. Suicide rates were nearly the same in both cohorts.

There was a slight excess of mortality from external causes among women Vietnam veterans compared with non-Vietnam veterans, primarily due to an excess of motor vehicle accidents. In comparison to U.S. women, mortality from cancers of the pancreas and uterine corpus was elevated among Vietnam veterans but the increase was not statistically significant.

**NVVRS Review Ongoing**

Project 2, the review of NVVRS data for women Vietnam veterans, is underway. Women Vietnam veterans are being evaluated by military service characteristics, including occupation, length of service, branch, rank, and career status. Investigators are considering and will adjust for other factors, including age, race, substance abuse, and family history of violence. The results will be submitted to a scientific journal and will be described in a future issue of the "Agent Orange Review."

**Reproductive Outcomes Study Approved**

Project 3, a study of reproductive outcomes among women Vietnam veterans, is the most complex of the research efforts planned and has required the longest time to gain approval.

A revised protocol was approved by the VA Central Office Research and Publication Committee in July 1991. Secretary Derwinski submitted the protocol to the OTA for its review in September. The OTA Scientific Advisory Committee reviewed it in November. VA received an approval letter from the OTA in December 1991.

The reproductive outcomes study will utilize a roster of women Vietnam veterans and non-Vietnam veterans identified for Project 1. The reproductive outcomes to be studied are infertility, spontaneous abortions, still births, live births with congenital malformations, infant deaths, birth weight, pre-term delivery and number of children. In addition, the relative risk of malignant tumors in female reproductive organs will be evaluated because mortality is not a reliable indicator of incidence for a certain cancer.

The workscope of the proposed study spans three years and involves collection and analysis of data on approximately 7,200 women veterans and their children. A pilot study of approximately 500 women veterans is planned. If the pilot study indicates that the response rate is unacceptably low, that self-reported responses are unreliable and biased, or that medical and vital records of participants and their children are not generally available for review, VA will determine the future course of action in consultation with the OTA and its own study oversight committee.

**About the "Review"...**

The "Agent Orange Review" is prepared by VA's Environmental Agents Service (EAS). The "Review" is published periodically to provide information on Agent Orange and related matters to Vietnam veterans, their families, and others with concerns about herbicides used in Vietnam. The most recent issue of the "Review" was published in December 1991.

The "Review" is prepared approximately one to two months prior to the publication date. This issue was written in February and does not include developments that occurred during March or April 1992.

Comments or questions about the content of the "Review" are encouraged. Suggestions and ideas for future issues of the newsletter should be sent to Donald J. Rosenblum, Writer/Editor, Agent Orange Review, Environmental Agents Service (116A), VA Central Office, 810 Vermont Avenue, NW, Washington, DC 20420.

Requests for additional copies of this issue, should also be directed to Mr. Rosenblum. Please specify the number of copies you are requesting. A limited supply of the last seven issues (October 1989, May 1990, August 1990, February 1991, April 1991, August 1991, and December 1991) is also available. VA facilities should order additional copies from the VA Supply Depot.

VA updates the "Review" mailing address listing annually. If you have not been filing Federal income tax annually and have moved to another residence, we may not have the best address for you and may not be able to send you future issues of the "Review." Therefore, if this is your situation, please send your old and new addresses and Social Security number to the Department of Veterans Affairs, Data Processing Center (200/397), 1615 East Woodward Street, Austin, Texas 78772.

If you have questions about your Agent Orange Registry examination, contact the Environmental Physician or Agent Orange Coordinator at the VA medical center where you had the examination. Questions about VA benefit programs, including disability compensation, should be directed to a veterans benefits counselor at the VA facility nearest you. The telephone number can be found in your telephone book under the "U.S. Government" listings.

**Ranch Hand Investigators Release Sixth Mortality Report**

In late December 1991, the U.S. Air Force Surgeon General released the sixth mortality review of the "Air Force
Health Study, an Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides."

This report is part of an ongoing investigation to determine if there are adverse health effects from herbicide exposure in Air Force veterans who conducted aerial spray missions in Operation Ranch Hand in Southeast Asia.

The report did not reveal any differences between the observed and expected number of Ranch Hand deaths from all causes. This finding is consistent with earlier results reported in 1983, 1984, 1985, 1986, and 1989.

The 1991 analysis did show, however, increased Ranch Hand deaths due to digestive diseases and, in non-flying enlisted personnel, circulatory system diseases. The increase in digestive deaths has been noted in the earlier studies. The increased number of deaths due to circulatory system diseases among the non-flying enlisted personnel is a new finding. Air Force investigators had no explanation for this latter increase, but they indicated that it is being investigated further.

The Air Force report contrasts the cumulative deaths among the Ranch Hand group of 1,261, with that of a comparison population of 19,080 Air Force veterans who flew or serviced C-130 cargo aircraft in Southeast Asia during the same time that the Ranch Hand unit was active in Vietnam.

This study is part of a planned 20-year effort. In addition to the six mortality reports, investigators have issued four morbidity reports. The results of the most recent morbidity analysis was released on March 29, 1991. The findings were described in the August 1991 issue of the "Agent Orange Review." Sequential questionnaires, medical record review and physical examinations will be conducted this year and in 1997 and 2002 to further assess health effects.

William H. Wolfe, M.D., M.P.H., is the principal investigator. The continuing research study is being conducted by the Armstrong Laboratory, Human Systems Division, Brooks Air Force Base, Texas. Additional information on this project can be obtained from the Office of the Air Force Surgeon General, Bolling Air Force Base, Washington, DC 20332-6188. The telephone number is (202) 767-5046.

Animal Research - Benefits and Limitations

The value of animal research has been discussed and debated by scientists worldwide for many years. There remains considerable disagreement about how data gathered in animal studies relate to humans. This article briefly reviews the potential benefits and limitations of animal research and urges readers to be cautious in interpreting the results of such studies. Our focus is on dioxin, but much of the discussion is relevant to other substances.

Dioxin, specifically 2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD, has been identified in some news media reports as one of the most deadly or toxic substances in the world. (TCDD is an unwanted by-product which developed in minute quantities during the manufacture of 2,4,5-T, one of the ingredients of Agent Orange.)

This characterization is based on results of laboratory tests on certain animals and has understandably alarmed many people, including Vietnam veterans who may have been exposed to dioxin. On the other hand, many scientists have concluded from other studies that dioxin does not have serious long-term health consequences for humans.

It is important to understand that toxic effects induced by TCDD vary significantly among different species. Guinea pigs are extremely sensitive to TCDD. To achieve the same level of toxicity in rabbits, bullfrogs, and hamsters, scientists need to administer doses of TCDD approximately 115,500, and 5,000 times as large, respectively, adjusted for body weights. (Researchers adjust for body weights by administering 16 times as large a dose for an animal that weighs a pound as for one weighing an ounce.)

Considerable care must be taken in interpreting results of animal studies because laboratory animals may respond very differently from humans in the way they absorb chemicals, in the distribution of these chemicals in the body, in the way the chemicals are broken down or stored in the body, and in the way they are eliminated. Differences in body size, diet, lifespan, and the way individual organs function may also cause animals to respond differently from humans.

The differences between species in the toxic dosage is complicated by the fact that different species reflect the toxicity of dioxin in different ways. Some species develop liver problems, others manifest kidney damage, while other species have different difficulties.

Responsible researchers are reluctant to base predictions of human health effects on animal studies unless the chemical has been tested in several species of experimental animals and there is a good scientific basis for believing that the test animals are similar to humans in the way they respond to the chemical.

Unfortunately, due to the wide variability of responses seen among the different species, scientists are unclear what these results suggest regarding the long-term health consequences of human exposure to TCDD.

Some observers have questioned the value of animal studies. Generally, studies are conducted prior to human exposure in an attempt to judge toxicity and/or to develop preventive measures. To gain some insight into what might occur in a "worst case scenario," scientists usually administer dosages to laboratory animals far in excess of what would be expected by humans. These laboratory experiments are designed to learn how and why a substance may affect humans. These studies are basically performed when studies cannot be done in humans.

Agent Orange was not tested in experimental animals at the time of its manufacture and use during the Vietnam Conflict because its two ingredients had previously been tested and had enjoyed extensive commercial and private use in the United States and in many countries around the world from the 1940's well into the 1970's. (One of these ingredients is still widely used in this country and abroad.)

There are significant limitations to animal studies. One major problem, described above, is the very different responses seen in different species. While many substances induce similar reactions in a wide range of animals, dioxin effects vary considerably. Unfortunately, it is unclear which of these species would serve as the most accurate model for human responses.

Another important problem with animal research is the inconsistency in results often seen between testing of treated tissues or cells and the whole organism. In some instances, the
results are the same or very similar. When they are very different, as they often are, the responses may raise more questions than they answer.

A third difficulty encountered in animal studies is the difference in doses administered. As noted above, the dose used in non-human research efforts is relatively high. Great caution must be exercised when interpreting data generated by this research, especially when estimates are made regarding human reactions.

Another limitation is the difference in the delivery of the substance being tested. For example, while laboratory animals can be directly given specific measured doses of dioxin, this is not done in many human studies. For example, humans are not intentionally exposed to dioxin. Rather, they have been exposed indirectly in industrial (that is, manufacturing) accidents, in occupational pursuits (that would include farming, forestry, and gardening), and in military operations (specifically, in Vietnam). In many, if not most, instances, the extent of human exposure is difficult or impossible to quantify.

While scientists often gain valuable insights from animal studies, genuine dangers exist when data obtained are not prudently interpreted. Because of the significant differences between laboratory and human research efforts, scientists should reach conclusions about the potential effects of a substance on humans only after all confounding variables can be eliminated or controlled and the resultant effects can be replicated in several species. Otherwise, it is quite possible that the conclusions may mislead the public and unduly alarm individuals who may have been exposed to the substance.

Scientists need to be particularly careful when sharing their findings with those who do not have extensive scientific training. Non-scientists may misinterpret the study results and may take the findings out of its original context. It is important to be mindful of the limitations of animal research as well as the benefits.

Q's and A's

The Q's and A's (Questions and Answers) feature of the "Review" responds to questions that have been received from various sources. Questions for future issues should be sent to Donald J. Rosenblum, Writer/Editor, Environmental Agents Service (116A), VA Central Office, 810 Vermont Avenue, NW, Washington, DC 20420. We cannot guarantee that all questions received will be used in this column.

The Federal Government is continuing to pursue expensive scientific studies and reviews regarding Agent Orange and the health problems suffered by Vietnam veterans. At the same time, the Government seems to be denying that Agent Orange exposure has caused or contributed to such problems for many veterans. Isn't this inconsistent?

Not really. Concerns have been raised about the possible long-term health consequences of exposure to Agent Orange and other environmental factors experienced by Vietnam veterans. The Federal Government, especially the Department of Veterans Affairs (VA), has a responsibility, an obligation to investigate this matter. Unfortunately such studies are expensive and very time-consuming.

VA has recognized that there is a significant statistical association between several conditions and exposure to herbicides that contain dioxin, including Agent Orange. These conditions include soft tissue sarcomas, chloracne, and peripheral neuropathy. Under certain circumstances, VA will provide compensation to veterans with these medical disabilities. Chloracne is the only condition that has been clearly established as a result of exposure to dioxin. VA also has recognized non-Hodgkin's lymphoma as service-connected for Vietnam veterans. Some scientists suspect that non-Hodgkin's lymphoma may be related to exposure to Agent Orange.

Ongoing research reflects the commitment of the Federal Government to explore all factors that may contribute to health problems experienced by Vietnam veterans. This continuing effort acknowledges that all the answers to the many questions raised by Vietnam veterans and others about this matter cannot yet be answered.

What herbicides other than Agent Orange were used in Vietnam? What other substances were sprayed in Vietnam?

Fifteen different herbicides were shipped to and used in Vietnam between January 1962 and September 1971. Most of the herbicide sprayed in Vietnam was Agent Orange, which was used between 1965 and 1970. Herbicides other than Agent Orange were used in Vietnam prior to 1965, but to a very limited extent. Agents White, Blue, Purple, Pink, and Green were all used in Vietnam.

The control of malaria and other diseases carried by mosquitoes in Vietnam necessitated an extensive aerial insecticide application program. From 1966 through 1972, three C-123 aircraft were used to spray Malathion. These aircraft routinely sprayed this insecticide adjacent to military and civilian installations, as well as in areas where military operations were in progress, or about to commence. Some veterans who suspect that they were sprayed with herbicides were actually exposed to insecticide.

Agent Orange Fact Sheet Series Updated

The Environmental Agents Service in VA headquarters in Washington, DC, recently updated and released a series of Agent Orange fact sheets, known as "Agent Orange Briefs."

The revised "Briefs," dated February 1992, describe a wide range of Agent Orange-related matters. The following "Briefs" are currently available: (A1) Agent Orange - General Information, (A2) Agent Orange Class Action Lawsuit, (B1) Agent Orange Registry, (B2) Agent Orange - Priority Treatment Program, (B3) Agent Orange and VA Disability Compensation, (B4) VA Information Resources on Agent Orange and Related Matters, (C1) Agent Orange - The Problem Encountered in Research, (C2) Agent Orange and Vietnam Related Research - VA Efforts, (C3) Agent Orange and Vietnam Related Research - Non-VA Efforts, (D1) Agent Orange and Birth Defects, (D2) Agent Orange and Chloracne, (D3) Agent Orange and Non-Hodgkin's Lymphomas, (D4) Agent Orange and Soft Tissue Sarcomas, and (D5) Agent Orange and Peripheral Neuropathy.
The "Briefs" were distributed widely throughout VA and to various State offices. Earlier versions of the "Briefs" were released in October 1988, October 1989, September 1990, and July 1991. Copies of the outdated issues are no longer available.

For additional information or a copy of the new fact sheets, contact the Agent Orange Coordinator at the nearest VA medical center or write to the Environmental Agents Service (116A), VA Central Office, 810 Vermont Avenue, NW, Washington, DC 20420.

Cacodylic Acid Monograph Available

In December 1985, VA published a technical monograph to provide a single source of information on cacodylic acid (CA) and its sodium salt (NaCA). A very limited supply of the 164-page book is still available. University libraries, researchers, and scientists interested in receiving a complimentary copy should write to the Environmental Agents Service (116A), VA Central Office, 810 Vermont Avenue, NW, Washington, DC 20420.

The monograph, entitled Cacodylic Acid: Agricultural Uses, Biologic Effects, and Environmental Fate, was authored by Ronald D. Hood, Ph.D., of the Department of Biology at the University of Alabama in Tuscaloosa, Alabama.

Cacodylic acid and its sodium salt were the active ingredients in Agent Blue, one of the group of herbicides used in Vietnam to defoliate hiding places, supply lines, and staging areas held by opposing forces. Along with phenoxy herbicides, Agent Blue was used experimentally in the early to mid-1960’s and more extensively from 1965 to 1970. As with the phenoxy herbicides, these organic arsenicals had been widely used in agriculture and forestry for many years with no known risk to human health.

The first five chapters focus on the very complex and highly technical aspects of the chemical and physical properties as well as the production, agricultural uses, and environmental considerations of cacodylic acid and its sodium salt. Chapters six through eight discuss pharmacology and toxicology issues, and the ninth (and final chapter) provides a summary overview and describes areas where additional research is needed.

The publication is written for use by scientists. Veterans without extensive scientific training would have considerable difficulty in understanding the text.

Class Action Lawsuit Referral Information

The Department of Veterans Affairs (VA) has received many inquiries regarding the status of claims for compensation from the Agent Orange Settlement Fund. This fund was established by a Federal court as a result of the settlement of a class action lawsuit ("Agent Orange" Product Liability Litigation) brought by Vietnam veterans and their families against the manufacturers of Agent Orange.

Neither VA nor any other Federal Executive Branch department or agency is directly involved in the distribution of the settlement funds. Information on this matter can be obtained by calling, toll-free 1-800-225-4712, or writing to the Agent Orange Veteran Payment Program, P.O. Box 110, Hartford, Connecticut 06104.