

IOM Identifies Link with Chronic Lymphocytic Leukemia, Principi Extends Benefits

On January 23, 2003, the National Academy of Sciences' Institute of Medicine (IOM) officially released the fifth comprehensive report in a series entitled *Veterans and Agent Orange*.

The latest report findings are similar to the earlier documents with one major change. *Update 2002* concludes that there is "sufficient evidence of an association" between herbicides used in Vietnam and chronic lymphocytic leukemia (CLL). Department of Veterans Affairs Secretary Anthony J. Principi has accepted this assessment, and ordered the development of regulations that would add CLL to the list of illnesses presumptively recognized for service connection among Vietnam veterans. VA will be able to begin paying compensation benefits once the regulations are finalized later this year.

Principi Acts

Secretary Principi asked key officials and scientists within and outside VA to evaluate the latest IOM report and advise him on appropriate action. On January 23, based on the recommendations he received and his reading of the report, the Secretary announced that CLL would be added to the list of presumptively recognized conditions for service connection.

"Compelling evidence has emerged within the scientific community that exposure to herbicides such as Agent Orange is associated with CLL," Principi declared. "I'm exercising my legal authority to ensure the full range of VA benefits is available to Vietnam veterans with CLL." The Secretary added, "On the modern battlefield, not all injuries are caused by shrapnel and bullets. This latest IOM study and my decision to act upon it are the latest examples of VA's continuing efforts to care for the needs of our combat veterans."

What the Decision Means

The Secretary's decision means that veterans with CLL who served in Vietnam during the Vietnam era don't have to prove that their illness is related to their military service to qualify for VA disability compensation. For more than 20 years, VA has offered special access to medical care to Vietnam veterans for health problems that may have resulted from Agent Orange exposure. (VA presumes that all Vietnam veterans were exposed to Agent Orange or other herbicides.) Secretary Principi's decision will ensure higher-priority access to care for those veterans with CLL.

Background

The initial IOM report, entitled *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, dated 1994, was released in 1993. Updates were

issued in 1996, 1999 (identified by IOM as *Update 1998*), and 2001 (dated 2000). In addition, the IOM has released two special reports on Agent Orange, one, published in 2000, regarding the possible association between herbicide exposure on diabetes, and another, published last year, on one type of childhood cancer.

In the latest comprehensive document, subtitled *Update 2002*, the IOM, a highly respected, independent, non-governmental scientific review organization working on behalf of the Department of Veterans Affairs (VA), evaluated all available scientific evidence from studies of veterans and other groups, to determine what health problems may be associated with exposure to Agent Orange and other herbicides used in Vietnam. VA requested that the IOM focus on CLL in *Update 2002* because of concerns raised by some veterans that CLL shares some similarities with non-Hodgkin's lymphoma, which has been recognized for service connection for several years.

Update 2002 was conducted by a 10-member committee of scientists, chaired by Irva Hertz-Picciotto, Ph.D., a professor in Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill. Michelle C. Catlin, Ph.D., a program officer in the IOM's Board on Health Promotion and Disease Prevention, was the Study Director.

The information that the committee reviewed was identified through a comprehensive search of relevant databases, including public and commercial databases covering biologic, medical, toxicologic, chemical, historical, and regulatory information. More than 9,000 potentially relevant studies were identified in the searches, and more than 1,000 were reviewed. The committee reported that input received from veterans and others interested persons at public hearings and in written submissions served as a valuable source of additional information.

IOM's Four Categories

In the latest report, the IOM assigned each health outcome considered in the report to one of four categories based on the amount and quality of scientific evidence of an association with Agent Orange or other herbicides used in Vietnam. This was the same procedure used for prior reports. In making the assignments, the IOM considered a large range of occupational, environmental, and veterans' studies.

The four categories are (1) sufficient evidence of an association, (2) limited/suggestive evidence of an association, (3) inadequate/insufficient evidence to determine whether an association exists, and (4) limited/suggestive evidence of no association.

Category 1 - Sufficient Evidence of an Association

The IOM included health outcomes in the first category when a positive association has been observed between herbicides and the outcomes in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.

In its initial report, the IOM included five illnesses in this category: soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, chloracne, and porphyria cutanea tarda (in genetically susceptible individuals). In the 1996 update, the IOM lowered porphyria cutanea tarda to the second category while the other conditions remained in the first. In the 1996, 1998, and 2000 updates, no additional health outcomes were included in this first category. The inclusion of CLL in this category marks the first time that a condition has been added to this category since the initial report was issued.

Category 2 - Limited/Suggestive Evidence of an Association

The IOM lists conditions in the second category when the evidence reviewed 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. Health outcomes are included in this category when, for example, at least one high quality study shows a positive association, but the results of other studies are inconsistent.

In the report released in 1993, the IOM included only three outcomes (respiratory cancers, prostate cancer, and multiple myeloma) in this category. Six health outcomes were included in this category in 1996 and 1998. In addition to these three cancers and porphyria cutanea tarda (mentioned above), the IOM cited acute and subacute transient peripheral neuropathy in Vietnam veterans and spina bifida in their children. The initial report listed peripheral nervous system disorders as a group in the third category.

In the 1996, 1998, and 2000 updates, the IOM distinguished between acute and subacute transient peripheral neuropathy and chronic peripheral nervous system disorders (which remained in the third category). Similarly, the IOM separated spina bifida from other birth defects (which remained in the third category).

In the special report on diabetes released in 2000, the IOM moved Type 2 diabetes from category three (inadequate/insufficient evidence to determine whether an association exists) to this one. In *Update 2000*, Type 2 diabetes remained in this category. In *Update 2002*, Type 2 diabetes is included in this category.

Another change in this category, made by *Update 2000*, was the addition of acute myelogenous leukemia (AML) in the children of Vietnam veterans. Under existing law, VA lacks authority to provide benefits or services to these children. AML was previously grouped with other childhood cancers in offspring. Careful analysis of U.S. and Australian studies led IOM to include this rare condition in category 2. However subsequent review by the IOM after Australian scientists discovered an error in their study, resulted in a downgrade to category 3 last year. (For more information on this reversal, see the front page article in the May 2002 issue of the Agent Orange Review), online at www.va.gov/agent_orange.

Category 3 - Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Most conditions evaluated in IOM's 2002 report (as well as in the earlier publications) were listed in their third category. The IOM placed health outcomes to this category when available studies are of insufficient quality, consistency, or power to permit a conclusion regarding the presence or absence of an association. Health outcomes for which there are no available studies would also fall into this category.

The following outcomes were listed in IOM category three in *Update 2002*: hepatobiliary cancers, nasal or nasopharyngeal cancer, bone cancer, breast cancer, female reproductive cancer (cervical, uterine, and ovarian), urinary bladder cancer, renal cancer, testicular cancer, leukemia (other than CLL), skin cancer, spontaneous abortion, birth defects (other than spina bifida), neonatal or infant death and stillbirths, low birthweight, childhood cancers in offspring, including acute myelogenous leukemia, abnormal sperm characteristics and infertility, cognitive and neuropsychiatric disorders, motor or coordination dysfunction, chronic peripheral nervous system disorders, metabolic and digestive disorders (changes in liver enzymes, lipid abnormalities, and ulcers), immune systems disorders (immune suppression and autoimmunity), circulatory disorders, respiratory disorders, and AL-type primary amyloidosis, endometriosis, and the effects on thyroid homeostasis.

The 1996 changes are the two noted above (that is, the separation of acute and subacute transient peripheral neuropathy from chronic peripheral neuropathy; and spina bifida from other birth defects) plus an elevation of skin cancer from the fourth category. Urinary bladder cancer was added to this category in 1998.

In *Update 2000*, as a result of the change for acute myelogenous leukemia, the health outcome "childhood cancer in offspring" was modified to exclude AML. However, as a result of subsequent revision, it was again included with other childhood cancers in this category where it remains in *Update 2002*.

For *Update 2000*, at VA's request, the IOM evaluated the possible relationship between herbicides used in Vietnam and AL-type primary amyloidosis, a condition similar in many ways to multiple myeloma (an illness in category 2). IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists. VA had received several letters from interested individuals suggesting a link with herbicide exposure. In the 2002 report, the IOM added an evaluation of endometriosis and the effects of thyroid homeostasis to this category.

Category 4 - Limited/Suggestive Evidence of *No* Association

Health outcomes are included in the fourth category when several adequate studies, covering the full range of levels of exposure that humans 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.

The 2002 report, like the 1996, 1998, and 2000 documents, puts the following

conditions in Category 4: gastrointestinal tumors (stomach, pancreatic, colon, and rectal cancers) and brain tumors. The only change in 1996 from the first report in this category was the elevation of skin cancer to the third category. The only change in 1998 was the elevation of urinary bladder cancer to the third category. In the 2000 and current updates, there is no change in this category compared with the 1998 IOM update.

Research Recommendations

In *Update 2002*, the IOM also offers several research recommendations. The committee suggests continuing of the Air Force Health Study of Operation Ranch Hand personnel (the unit involved in the aerial spraying of Agent Orange), expanding the studies of Army Chemical Corps veterans, and following the experience of Vietnam veterans as they age, with emphasis on diseases associated with aging.

The committee also concludes that certain rare tumors are worthy of further investigation despite previous evidence of *no* association. The committee supported steps that would continue development of collaborative research programs between U.S. and Vietnamese scientists.

Required by Public Law 102-4

Under Public Law 102-4, the Agent Orange Act of 1991, within 60 days after the Secretary of Veterans Affairs receives a report on the possible long-term health effects of Agent Orange and other herbicides used in Vietnam from the National Academy of Sciences' IOM, the Secretary must determine whether a presumption of service connection is warranted for each disease covered by the report. If the Secretary concludes that a presumption of service connection is warranted, he or she must issue regulations within 60 days of this determination.

Within 90 days after the Secretary issues any proposed regulations regarding these diseases, the Secretary must issue final regulations. Such regulations are effective the day of issuance.

If the Secretary determines that a presumption of service connection is not warranted, he or she, within 60 days of the making the determination, must publish in the *Federal Register* a notice of that finding. The notice must include an explanation of the scientific basis for the determination.

Earlier VA Responses

IOM reports on Agent Orange have had a significant impact on VA compensation policy, as documented in the next four paragraphs.

The 1993 and 1996 IOM reports resulted in substantial changes in VA policy. On July 27, 1993, the day the IOM released its first report, then VA Secretary Jesse Brown

announced that Hodgkin's disease and porphyria cutanea tarda would be added to the list of conditions presumed to be service-connected for veterans exposed to herbicides in Vietnam. (VA presumes that all Vietnam veterans were exposed to such herbicides).

Two months later, after further review of the IOM document, Secretary Brown announced that multiple myeloma and respiratory cancers would be added to the list of conditions presumed to be service-connected for veterans exposed to herbicides in Vietnam.

After reviewing the 1996 IOM update, Secretary Brown concluded that acute and subacute transient peripheral neuropathy (if manifested within 1 year of exposure to an herbicide in Vietnam and resolved within 2 years of onset) and prostate cancer should and would be added to the list of conditions presumed to be service-connected for veterans exposed to herbicides in Vietnam.

In 1996, when the IOM found an association between herbicides used in Vietnam and the birth defect spina bifida in the children of Vietnam veterans, VA sent draft legislation to Congress (enacted, with modification, as part of Public Law 104-204 in September 1996) to provide for certain benefits and services for these children.

Update 1998 and *Update 2000* did not result in changes in compensation policy. The IOM's special 2000 report on Type 2 diabetes resulted in that condition being added to the list of presumptively recognized conditions for service connection.

As a condition in Category 1, CLL was a relatively easy and non-controversial call under the guidelines established by Congress. Historically, all conditions in that category have promptly been recognized for service connection. All illnesses in the second category have ultimately been recognized as well.

Report on the Internet, Also Available for Purchase

Copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055. The telephone numbers are (toll-free) 1-800-624-6242 and (in the Washington, DC, metropolitan area) 202-334-3313. The Internet address is www.nap.edu.

IOM Reports Will Continue

The IOM will be re-evaluating existing scientific evidence and assessing new information regarding the possible long-term health consequences of herbicide exposures. Based upon the results of the most recent report, VA has requested that the IOM take a careful look at other forms of leukemia in their next update, due in 2004.

The IOM was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under responsibility given to the Academy by its congressional charter to be an adviser to the Federal

Government and, upon its own initiative, to identify issues of medical care, research, and education. For information about the IOM, see www.iom.edu.

The January 23, 2003 VA news release on the Secretary's action related to CLL can be found at www.va.gov/opa.