INSTITUTE OF MEDICINE UPDATE ON VETERANS AND AGENT ORANGE

HEARING

BEFORE THE

SUBCOMMITTEE ON
HOSPITALS AND HEALTH CARE

OF THE

COMMITTEE ON VETERANS' AFFAIRS
HOUSE OF REPRESENTATIVES

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INSTITUTE OF MEDICINE UPDATE ON VETERANS AND AGENT ORANGE

TUESDAY, APRIL 16, 1996

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC.

The subcommittee met, pursuant to call, at 10 a.m., in room 334, Cannon House Office Building, the Hon. Tim Hutchinson (chairman of the subcommittee) presiding.

Present: Representatives Hutchinson, Smith, Stearns, Fox, Edwards, Kennedy, Tejeda, Gutierrez, Bishop, and Brown.

Also Present: Representative Evans.

OPENING STATEMENT OF CHAIRMAN HUTCHINSON

Mr. HUTCHINSON. The subcommittee will come to order.

Today the subcommittee meets in its oversight role to hear testimony on the recently released update by the Institute of Medicine on an association between herbicides and diseases in veterans who served in Southeast Asia.

The update is in response to the congressionally mandated requirement of the Agent Orange Act of 1991, which requires the National Academy of Sciences to conduct an independent, comprehensive review, and critical evaluation of the scientific studies and medical evidence concerning the health effects of herbicide exposure. Reviews are required under the Act every 2 years.

The study released by the Institute of Medicine as a reevaluation of the Agent Orange Health questions identified two new health effects in the category of a limited or suggestive association between herbicide or dioxin exposure. They are the acute transient form of peripheral neuropathy, a neurological disorder that can lead to pain, numbness, and weakness in the limbs in Vietnam veterans, and spina bifida, a congenital abnormality in their children.

I would like to begin by stating that the Veterans' Affairs Committee has historically demonstrated a longstanding record of bipartisan support for those veterans who so nobly served this country during possibly the most politically turbulent period in our nation's history. Five members of the full committee are veterans of this era. I would like to recognize the service of Mr. Stearns, Mr. Bachus, Mr. Evans, Mr. Clement, and Mr. Tejeda.

Over the years individual members of the committee, such as Lane Evans, have committed themselves to the resolution of issues affecting what is now the largest cohort of living veterans, the 8.5 million veterans of Vietnam and the Vietnam Era.

This morning we are fortunate to have on our first panel a group of eminent researchers, two of which, Drs. David Erickson and Joel Michalek, are authors of two seminal studies on Agent Orange. These are the 1984 Vietnam veterans' risks for fathering babies with birth defects, and the ongoing Ranch Hand study.

I also would like to welcome Dr. David Tollerud, Chairman of the Institute of Medicine Committee to review the health effects in Vietnam veterans, and Dr. Andrew Olshan, a member of the committee who is a nationally recognized expert on reproductive health effects.

I would like to personally thank each of the members of the committee who served on the Institute of Medicine Committee to review the health effects of Vietnam veterans. Service on this committee, as I understand it, was completely voluntary and without compensation, and you are to be thanked and to be commended.

The questions of cause and effect relationships between exposure to herbicides, such as dioxin, and service in Vietnam have from the very beginning been mired in controversy. The questions asked of the experts have been simple, but finding the real answers have been long in coming.

The experts before this subcommittee today have spent countless years looking at the complexity of the problems posed by exposures to various chemical agents and their possible effects on the environment and its inhabitants. This hearing is not an attempt to reach a final verdict on the issues raised by the IOM update, but it is an important step in ascertaining the possible needs for further congressional action.

It should be understood that the Agent Orange Act of 1991 requires the Secretary of Veterans Affairs within 60 days of release of the Institute of Medicine report to determine whether additional presumptions of service connection are warranted for any of the diseases covered in the report.

The recommendations of the VA Task Force and any subsequent action of the Secretary relates only to service connection of diseases suffered by veterans themselves. Nothing in the Act governs policy decisions regarding health effects in the offspring of veterans. Such a change would require congressional action.

So the purpose of this hearing is to help us determine whether such action is warranted.

The chair recognizes now my friend and colleague, the Ranking Minority Member, Chet Edwards, for his opening remarks.

OPENING STATEMENT OF HON. CHET EDWARDS

Mr. EDWARDS. Thank you, Mr. Chairman.

Mr. Chairman, I want to commend and thank you for responding so quickly to the recent publication of the Institute of Medicine report on Agent Orange and scheduling this hearing. You really have assembled an impressive line-up of witnesses.

I hope the testimony we receive today will not only help us understand the report's findings and implications, but most importantly, assist us in determining what our next step should be.

Among its most striking findings, the IOM reported that there is new, limited or suggestive evidence to show an association between exposure to herbicides and the congenital birth defect spina bifida.

This finding has undoubtedly bolstered the hopes and expectations of numbers of veterans and their families potentially affected.

Yet the IOM report concedes that the evidence for such an association is inconclusive, and that, quote, the pattern warrants further evaluation.

I welcome the opportunity to learn where there is any promise or hope for further, more conclusive research or analysis and what the prospects are for conducting such research or analysis in the near term.

Mr. Chairman, this hearing is a first step and a very important first step, and I want to thank you for scheduling it.

Mr. HUTCHINSON. Thank you, Mr. Edwards.

The chair would now recognize any subcommittee member who might have an opening statement. Mr. Tejeda, do you have an opening statement?

Mr. TEJEDA. No, but I certainly welcome them and look forward to hearing what they have to say, and I certainly thank the Chairman for putting this together.

Thank you very much.

Mr. HUTCHINSON. Mr. Gutierrez.

Mr. GUTIERREZ. Mr. Chairman, I would like my opening statement to be entered into the record and to then move forward to listen to the witnesses.

[The prepared statement of Congressman Gutierrez appears on p. 56.]

Mr. HUTCHINSON. Without objection, it will be entered into the record.

Mr. GUTIERREZ. Thank you, Mr. Chairman.

Mr. HUTCHINSON. Mr. Stearns, did you have an opening statement?

Mr. STEARNS. Mr. Chairman, I just commend you for these hearings, and also I would like to make my opening statement part of the record.

[The prepared statement of Congressman Stearns appears on p. 59.]

Mr. HUTCHINSON. Without objection.

I am sorry. Mr. Evans, we are glad to have you join the subcommittee today. We appreciate your very great interest in this.

OPENING STATEMENT OF HON. LANE EVANS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. EVANS. Thank you, Mr. Chairman, and I am not a member of the subcommittee. So I appreciate you inviting me to participate.

I want to thank you for holding this important hearing. I think it is very essential at this time to look into this issue. I hope that this will just be the beginning of hearings on this important issue. I think in the near future we need to hear from the veterans and families themselves, as well as service providers that have assisted veterans whose children are coping with spina bifida. I appreciate what you are doing today. I hope we can follow up in that regard.

And I appreciate your giving me the opportunity to speak, and I would like to enter the rest of my statement into the record

[The prepared statement of Congressman Evans appears on p. 65.]

Mr. HUTCHINSON. Without objection.

Mr. Kennedy, do you have an opening statement?

Mr. KENNEDY. Nothing other than to welcome the panel.

Mr. HUTCHINSON. We are glad you could be here.

Mr. KENNEDY. I look forward to your testimony.

Mr. HUTCHINSON. Okay. Thank you, Joe.

The chair now recognizes our first panel. I would ask that each witness summarize your testimony. The full text will be entered into the record. The order of the witnesses: Dr. David Tollerud, we would ask you to begin, then Dr. Olshan, Dr. Erickson, Dr. Michalek. Dr. Tollerud.

STATEMENT OF DAVID TOLLERUD, M.D., ASSOCIATE PROFESSOR AND CHIEF, OCCUPATIONAL AND ENVIRONMENTAL MEDICINE, UNIVERSITY OF PITTSBURGH

Dr. TOLLERUD. Thank you.

Good morning, Mr. Chairman and members of the committee. My name is David Tollerud. I am Associate Professor and Chief of the Division of Occupational and Environmental Medicine at the University of Pittsburgh.

I was the chair of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. This committee, as you have noted, was organized under the auspices of the Institute of Medicine, a nonprofit organization that provides health policy advice under congressional charter to the National Academy of Sciences.

I will begin by briefly explaining the content of the report, the intent of the report written by our committee, and reviewing its major findings. Then Dr. Andrew Olshan, a member of the Committee with specific expertise in reproductive health effects, will go into more detail regarding the findings on spina bifida and other reproductive outcomes.

For Vietnam veterans and their families, the issue of Agent Orange exposure has been a source of great anguish. The goal of the first study in response to the Agent Orange Act of 1991, which was also conducted by a committee of the Institute of Medicine, was to establish an agreed upon base of information from which to proceed to answer specific questions. The Agent Orange Act specified that this information base should be updated every 2 years.

The information we are discussing today was developed for the first update of that report, which incorporates new scientific information that has become available since the initial study. As part of our testimony, we are submitting a copy of the executive summary of the report, which we ask to be included in the record.

(See p. 73.)

Mr. HUTCHINSON. Without objection, it will be entered into the record.

Dr. TOLLERUD. The Committee studied both the toxicological and epidemiologic data on herbicide exposures. After reviewing a large number of studies, we focused on approximately 35 new epidemiologic investigations for detailed review and analysis. Most of these studies were of people who were exposed to herbicides or dioxin as a result of their jobs or as a result of contact in the environment, for example, because of a nearby industrial accident.

However, as Dr. Olshan will detail, the information on reproductive health effects came primarily from studies of Vietnam veterans themselves. I should emphasize that the Committee's analysis was limited to the types of herbicides used in Vietnam and to the contaminant dioxin.

In conducting its study, the Committee operated independently of the Department of Veterans Affairs and other government agencies. It was not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure.

The Committee was charged with reviewing the scientific evidence rather than making recommendations regarding policy, and the Committee's findings are not intended to imply or suggest any policy decisions. These must rest with the government.

Instead the study provides scientific information for the Secretary of Veterans Affairs and others to consider as they exercise their responsibilities to Vietnam veterans.

The Committee classified diseases into four categories following the form of the first report, and I would refer you to Table 1.1 in the executive summary for a list of these categories and of the health conditions associated with them.

The first category shows sufficient evidence of a statistical association between the disease and exposure to herbicides and dioxin.

The second category, there was limited or suggestive evidence.

In the third category, there was inadequate or insufficient evidence to determine whether an association exists.

And in the fourth category, there was limited or suggestive evidence of no association.

Consistent with the mandate of the Agent Orange Act, the distinctions between categories are based on statistical association, not on causality. As a result, the Committee did not apply the standard criteria epidemiologists use when judging whether a causal relationship exists between an exposure and a health outcome.

The findings in the 1996 update are based on all of the available evidence, but the analysis concentrates on new evidence published since the first report.

Based on the evaluations, the Committee found sufficient evidence of a statistical association between exposure to herbicides or dioxin and three types of cancer: soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. We also found sufficient evidence of an association with chloracne, a skin condition.

The Committee found limited or suggestive evidence of an association between exposure to herbicides or dioxin and three other types of cancer: respiratory cancers, prostate cancer, and multiple myeloma.

The Committee noted two new health effects in the category of limited or suggestive evidence of an association between the herbicide or dioxin exposure. One is the acute transient form of peripheral neuropathy, a nerve disorder that can lead to pain, numbness, and weakness in the limbs.

The other is a congenital birth defect called spina bifida in the children of fathers who were exposed to herbicides. The results of three studies of Vietnam veterans suggest that a father's exposures to herbicides may put his children at greater risk of spina bifida,

which is characterized by a deformity of the spine and spinal cord and can cause neurologic problems.

For most of the other cancers, diseases, and conditions reviewed by the Committee, the scientific data were not sufficient to determine whether an association exists. These include a broad range of birth defects other than spina bifida.

The greatest problem that the Committee encountered was a severe lack of information about the exposure of individual Vietnam veterans to herbicides. We simply do not know enough about the exposure of individual veterans to determine to what degree they were or are at risk.

The IOM will continue to work with the Department of Veterans Affairs on this issue, especially in a recently initiated project on historical exposure reconstruction that follows up on the research recommendations in the 1994 report.

As we said when we issued the first report, we know that this will not end the controversy, but we hope that these additional findings will lead to a better understanding of the questions that remain and the steps we must take to answer them.

I would now like to ask Dr. Olshan to speak with you about the Committee's findings on the association between herbicide or dioxin exposure and adverse reproductive outcomes.

[The prepared statement of Dr. Tollerud, with attachment, appears on p. 66.]

Mr. HUTCHINSON. Dr. Olshan, you are recognized.

STATEMENT OF ANDREW OLSHAN, M.D., ASSISTANT PROFESSOR, DEPARTMENT OF EPIDEMIOLOGY, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA

Dr. OLSHAN. Thank you.

Good morning, Mr. Chairman and members of the committee. My name is Andrew Olshan, and I am an Assistant Professor of Epidemiology at the School of Public Health of the University of North Carolina at Chapel Hill.

One of the tasks of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides was to review the published scientific literature on exposure to herbicides and adverse reproductive and developmental effects, focusing on studies published since the 1994 veterans and Agent Orange report. This literature included a number of studies that evaluated herbicide exposure and the risk of adverse outcomes, including miscarriages, birth defects, stillbirths, neonatal and infant mortality, low birth weight, and sperm quality and infertility.

The primary emphasis of the original report and the present review is on the potential adverse reproductive and developmental effects of herbicide exposure for males because the vast majority of Vietnam veterans are men.

The Committee examined studies of reproductive problems of men exposed to herbicides or dioxin as a result of their occupation, exposures in the environments, or service in Vietnam. For many of the outcomes, there was inadequate or insufficient evidence to determine whether an association exists. These include altered sperm parameters, infertility, miscarriage, stillbirth, and cancer in their children.

There is inadequate or insufficient information to determine whether an association exists between exposure to herbicides or dioxin and most birth defects. However, recently published results of a study of the offspring of veterans who participated in the Operation Ranch Hand Spraying Program suggests the possibility of an association between dioxin exposure and the risk of a particular group of birth defects collectively called neural tube defects. Anencephaly and spina bifida are two of the most common of the neural tube defects. Anencephaly is a general absence of a major portion of the brain, skull, and scalp. It almost always results in death within the first week after birth. Spina bifida is an incomplete closure in the spinal column.

The studies examined by the Committee addressed the more severe of the major types of spina bifida in which a portion of the spinal cord protrudes through the back at birth. This type is generally called spina bifida cystica.

Most infants born with spina bifida grow to adulthood with varying degrees of paralysis. In the general population in the U.S., spina bifida without anencephaly is seen in about five out of every 10,000 live births.

Some studies of veterans appear to show an elevated relative risk for either service in Vietnam or estimated exposure to herbicides or dioxin and neural tube defects in their offspring. On the basis of the pattern of findings in these studies, the Committee concluded that there was limited or suggestive evidence of an association between exposure to herbicides or dioxin and spina bifida.

For outcomes in this category, the evidence must be suggestive of an association with herbicides or dioxin, but limited because chance, bias, and confounding could not be ruled out with confidence. Typically at least one high quality study must indicate a positive association, although the results of other studies may be inconsistent.

For spina bifida, the Committee gave particular attention to the results of three studies it found to be of high overall quality: the Ranch Hand study, the Centers for Disease Control Birth Defect Study, and the CDC Vietnam Experience Study.

In the Ranch Hand study, spina bifida and anencephaly were increased among the offspring of veterans who were studied, with four total among the 792 live births to Ranch Hands in contrast to none in the comparison group of 981 live births to Air Force veterans who were not involved in the spraying program. The Ranch Hand veterans were classified according to estimates of their dioxin exposure based on their blood levels of dioxin.

Of the four infants with neural tube defects, three had spina bifida, and one had anencephaly.

The validation of self-reported birth defects in the study was systematic and of high quality, and the study controlled for an array of other factors.

The CDC Veterans Experience Study found that more Vietnam veterans reported that their children had a central nervous system anomaly than did non-Vietnam veterans. A sub-study was conducted as an attempt to validate the reported defects, including spina bifida and anencephaly, by examination of hospital records.

A difference was detected, but its interpretation was limited by various reporting and data validation problems.

The CDC birth defects study utilized the population based birth defects registry system in the metropolitan Atlanta area. There was no association between overall Vietnam veteran status and the risk of spina bifida or anencephaly. However, when an estimate of herbicide exposure opportunity based on dates and location of service was used in analysis, there was an association between an increased risk of spina bifida and higher exposure potential. There was no similar pattern of association for anencephaly.

This study has a number of strengths, including the use of a population based birth defects registry system and adjustment for a number of other factors that might have affected the risk of birth defects.

The study limitations include the relatively low response rates among individuals being surveyed, the time lag between birth and interview for some study participants, and imprecise exposure measurement.

Thus, taken as a group, the three epidemiologic studies suggest an association between herbicide exposure and increased risk of spina bifida in offspring. Although the studies were judged to be of relatively high quality, they do suffer from methodologic limitations, including recall bias, nonresponse bias, small sample size, and misclassification of exposure and outcome.

In addition, the failure to find a similar association with anencephaly, an embryologically related defect, is of concern.

Thank you for your attention, and Dr. Tollerud and I would be happy to answer your questions.

Mr. HUTCHINSON. Dr. Erickson.

STATEMENT OF DAVID ERICKSON, D.D.S., H.P.H, Ph.D, CHIEF, BIRTH DEFECTS AND GENETIC DISEASES BRANCH, NATIONAL CENTER FOR ENVIRONMENTAL HEALTH, CENTERS FOR DISEASE CONTROL AND PREVENTION

Dr. ERICKSON. Thank you, Mr. Chairman. I am pleased to be here.

My name is Dave Erickson. I am the Chief of the Birth Defects and Genetic Diseases Branch at CDC, and I am here to talk to you about two studies on birth defects that CDC has done relative to Vietnam veterans.

Dr. Olshan has just told you a little bit about spina bifida, and I can point out that at the back of my prepared testimony I have a diagram of an infant with spina bifida. In addition, there is a diagram of a fetus with anencephaly. Anencephaly is a related malformation to spina bifida, and is characterized by improper formation of the skull and brain.

Dr. Olshan pointed out that children with spina bifida can survive. Babies born with anencephaly are either stillborn or die shortly after birth.

Our first study of birth defects in Vietnam veterans was published in 1984 and was based on data collected from families of babies born in the metropolitan Atlanta area. Since 1967, CDC has gathered information on babies born with birth defects in the five-county area surrounding the City of Atlanta.

This surveillance program identified 5,000 babies born with birth defects from 1968 through 1980, with major structural defects. In our study, we compared the percentage of fathers in this group who have served in Vietnam with the percentage among fathers of 3,000 babies who were born without birth defects. If Vietnam veterans, in general, had been at increased risk of fathering babies with birth defect, we would expect to have found a higher proportion of Vietnam veterans among the fathers of babies with birth defects than among the fathers of babies born without birth defects.

What we found, however, was that 9.2 percent of fathers of babies with birth defects had served in Vietnam in the military compared with 9.5 percent of fathers of babies born without defects.

Similarly, this study showed that Vietnam veterans in general were not at increased risk of fathering babies with spina bifida or anencephaly.

At the time that our Atlanta study was done, there was no feasible laboratory method for measuring veterans' exposure to herbicide, Agent Orange or its suspected toxic contaminant dioxin. Thus, to try to evaluate the possible role of these compounds in the occurrence of birth defects among the children of Vietnam veterans, we had to rely on other, much less rigorous methods.

In an attempt to evaluate the possible connection between Agent Orange and birth defects, we constructed an index of opportunities for exposure to Agent Orange based on Vietnam veterans' military occupations, places, and times of service in Vietnam. We found no association between greater opportunities for exposure and overall risk of father a baby with all types of birth defects combined.

However, fathers who had greater opportunities for exposure as estimated by our index did have seemingly a higher risk of fathering a baby with spina bifida. We found no similar association with the risk for fathering babies with anencephaly.

Because of substantive uncertainties about the accuracy of the index, we were inclined to be skeptical about the finding. This inclination was strengthened by the lack of a parallel association with the related defect, anencephaly.

It is also worth mentioning today that later work with a different group of veterans showed no correlation of scores on a similar index and serum dioxin levels.

The second CDC study related to birth defects was the reproductive and child health component of the Vietnam experience study which rates the birth defects among babies fathered by about 7,900 Vietnam veterans were compared with the rates among babies of about 7,400 control veterans who did not serve in Vietnam.

The veterans who participated in this study had all served in the Army and came from all parts of the United States.

According to the information obtained in a telephone interview with veterans, six and a half percent of nearly 13,000 babies fathered by Vietnam veterans had birth defects compared to about five percent of nearly 12,000 babies fathered by control veterans. Notable among the defects were anencephaly and spina bifida. They were reported in about one in 1,000 of the babies of Vietnam veterans, but only one in 2,000 babies of control veterans.

Because of these findings, two sub-studies were added as components of the VES study. A general birth defects study, which was

a review of records, showed that there was no substantive difference in the rates of birth defects recorded in medical records of Vietnam veterans as compared to control veterans. In a cerebral-spinal malformation sub-study, a difference in the rate of confirmed spina bifida and anencephaly was noted. It was higher among the Vietnam veterans' babies than the control veterans, but there were a number of problems with this particular study.

An important limitation of these studies is that no information on the potential exposure to Agent Orange was collected.

Nevertheless, it was interesting that both CDC studies had some potentially suggestive, but highly equivocal findings relative to spina bifida.

You will hear soon about the results of spina bifida and anencephaly from the Air Force Ranch Hands study, and these findings have further raised our interest, but the accumulated evidence is far from proving a cause and effect relationship between exposure to Agent Orange and spina bifida.

The causes of most birth defects are unknown, and more research is needed to identify causes so that these devastating problems can be prevented in the future. While we're at present left with many questions about Vietnam veterans' risks for having babies with spina bifida, the past decade has witnessed a major breakthrough in our understanding of how a large fraction of spina bifida and anencephaly cases can be prevented.

I want to close by telling you a bit about this research success story and, in particular, how CDC's Atlanta Vietnam veterans study played a critical role in the establishment of this breakthrough.

Questions were included in the study about maternal vitamin use in the interviews. Analysis of the vitamin use data showed that women who used vitamins had a much lower risk for having a spina bifida or anencephaly affected pregnancy.

This finding was an important, unexpected benefit of our Vietnam veterans' birth defects study. We now know that if women consume 400 micrograms of the B vitamin folic acid before conception and during early pregnancy on a daily basis, their risk for having a pregnancy affected by spina bifida or anencephaly can be cut in half.

In the latest development in this tremendous story, the Food and Drug Administration has recently mandated fortification of cereal grain flours with folic acid to help women reach the recommended level of consumption. Although we have been unable to provide definitive answers about Vietnam veterans' risks for fathering babies with spina bifida, the studies conducted have contributed to the discovery of a tremendous prevention opportunity for these same defects.

That concludes my testimony. I thank you, and I would be happy to answer questions.

[The prepared statement of Dr. Erickson, with attachment, appears on p. 104.]

Mr. HUTCHINSON. Dr. Michalek.

STATEMENT OF JOEL E. MICHALEK, Ph.D., ARMSTRONG LABORATORY, EPIDEMIOLOGIC RESEARCH DIVISION, POPULATION RESEARCH BRANCH, DEPARTMENT OF THE AIR FORCE ACCOMPANIED BY COL. GARY HENRIKSEN, ARMSTRONG LABORATORY, HUMAN SYSTEMS CENTER

Dr. MICHALEK. Good morning, Mr. Chairman, members of the committee.

I am Joel Michalek, principal investigator of the Air Force Health Study, Armstrong Laboratory, Human Systems Center, Brooks Air Force Base, Texas. With me today is Colonel Gary Henriksen, principal investigator of the study.

I have prepared a brief review of our study and findings to date to bring you up to date on our efforts.

The Air Force health study is a 20-year, comprehensive assessment of the health, survival, and reproductive outcomes of 1,098 Air Force veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of herbicides in Vietnam from 1962 to 1971. Ranch Hand veterans were exposed to dioxin during their spray missions or by handling bulk quantities of Agent Orange and other herbicides.

The comparison group of 1,549 Air Force veterans who also served in Southeast Asia during the same period, but who were not involved with spraying herbicides serve as a control group. Comparison veterans were matched to Ranch Hands on age, race, and military occupation. All Ranch Hand veterans and comparisons are men.

Physical examinations were performed and questionnaires administered in 1982, 1985, 1987, and 1992. Additional examinations are planned for 1997 and 2002.

Reproductive experiences were assessed in the first Air Force health study report in 1984. The analyses of reproductive outcomes contained in that report are based on birth defects reported in 1982 by the mothers of the children. Those reports were not verified because the necessary medical records were not available at that time.

Record retrieval and verification took place between 1985 and 1990. In 1982, 1985, and 1987, participants were asked to provide access to medical records documenting each conception and the health of each child through the age of 18. This task involved the collection of medical records on 9,921 conceptions, including 8,100 live births.

During the same period, the Centers for Disease Control developed an assay for dioxin in sera that replaced the usual measuring of adipose tissue obtained by biopsy. In 1987, all Ranch Hands and comparisons were asked to donate blood for a dioxin measurement.

In 1990, we began analyzing verified reproductive outcomes versus direct body measurements of dioxin in our study subjects. That first round of analyses concluded in 1991 with a report released in 1992. That report included analyses of sperm counts and abnormalities, birth weight, miscarriages, abnormally low birth weight, birth defects, birth defect severity, developmental disabilities, and neonatal and infant mortality.

During the period 1992 through 1994, we updated our data files based on new information collected during the 1992 physical exam-

ination and reanalyzed spontaneous abortions, stillbirths, birth defects, birth defect severity, delays in development, and hyperkinetic activity, and in collaboration with CDC, summarized the results in an article. The article was accepted for publication in 1994 and published in 1995. That paper, entitled "Paternal Dioxin and Reproductive Outcomes Among Veterans of Operation Ranch Hand," is an attachment to this statement for the record.

(See p. 117.)

Mr. HUTCHINSON. That will be entered without objection.

Dr. MICHALEK. Thank you.

To summarize the results of our birth defect study, we found no statistically or biologically meaningful elevation in risk for spontaneous abortion or stillbirth. The term, "biologically meaningful," indicates that there is scientific data or literature to support the validity of an association. In the analysis of birth defects, we found elevations in risk in some organ system categories which, after review of the clinical descriptions, were found to be not biologically meaningful. There was an increase in nervous system defects in Ranch Hand children with increased paternal dioxin, but it was based on sparse data. We found no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin. We concluded that these data provided little or no support for the theory that paternal exposure to Agent Orange and its dioxin contaminate is associated with adverse reproductive outcomes.

As the Ranch Hand and comparison veterans continue to have children, we periodically reanalyze the data to reassess all of these conditions versus paternal dioxin level and will continue to do so during the course of the study.

Additionally, we have released data files without personal identifiers on health and mortality of the study participants to the public through the National Technical Information Service, Springfield, VA, and are preparing the reproductive outcome data for public release through NTIS.

In conclusion, I want to make a few remarks about our findings on spina bifida. Our study identified three children with spina bifida born to Ranch Hand veterans, while none of the comparison children had spina bifida. The three Ranch Hand fathers had elevated serum dioxin levels. These results seem unusual, but the sparseness of the data limited our ability to assess the significance of the association.

The Institute of Medicine has recently interpreted available evidence on spina bifida and exposure to herbicides as suggestive of an association, but limited because chance, bias, and confounding could not be ruled out with confidence.

The results of our study of Ranch Hand and comparison veterans were apparently important to the Institute of Medicine. However, it is my opinion that the accumulated evidence does not yet establish that there is a cause and effect relationship between herbicide exposure and spina bifida.

Thank you for giving me the opportunity to be here today, and I will be glad to answer any questions you have about the study.

[The prepared statement of Dr. Michalek, with attachment, appears on p. 112.]

Mr. HUTCHINSON. Thank you, Dr. Michalek.

Let me begin the questions. Thank all of you for your testimony. We appreciate it very much.

Dr. Tollerud, the requirement of the 1991 law is that information be updated every 2 years. What do you see as the next step in the process, and particularly if you would address the issue of the findings on spina bifida? Where do we go from here?

Dr. TOLLERUD. Sure. Well, first of all, I think with respect to the Agent Orange question and the dioxin question more broadly, there is significant hope that a new activity recently initiated by the Institute of Medicine to look at these historical reconstruction models and attempt to go back and look at databases developed subsequent to the Vietnam War on spray patterns and troop movements may be able to help shed more light on exposures of groups of veterans and sort out some of the health effects. So I think there is some optimism there.

With respect to the general activity of reviewing the data every 2 years, there have been a number of discussions within the Institute of Medicine and with the Department of Veterans Affairs suggesting that while the activities should continue, there may be different ways of looking at it, and in fact, our committee was cautiously optimistic that there may, in fact, be something to be gained from reanalyzing large databases that are already available from different investigators, and that perhaps one function of the IOM and of this effort might be to bring those investigators together with other investigators with different expertise.

Newer computer modeling programs have been developed, and then, in fact, more information can be extracted from additional data, and that would have the advantage of not having to launch a whole new study. So I think there is a lot of interest in perhaps pursuing that line. It would be a very much quicker and more effective way, I think, of generating new information.

Mr. HUTCHINSON. And that would be ongoing, not waiting 2 years for another report?

Dr. TOLLERUD. Right, right.

Mr. HUTCHINSON. With respect to the very academic statements that were made, could the panel explain or, Dr. Tollerud, let me leave it with you, in layman's language what the terminology "limited or suggestive evidence of an association between herbicide or dioxin exposure" means?

I kept hearing testimony that, well, this is not causal. We cannot go to a cause and effect in the limited or suggestive evidence of an association. Does that terminology have any scientific meaning?

Dr. TOLLERUD. It has scientific meaning in that the way the Committee evaluated the evidence, and the way the Committee placed or judged that certain health effects belong in different categories was based on published scientific information.

The nature of epidemiology and of science in this area is not precise, and the mandate of the Committee was not to limit itself to cause and effect relationships. Our job was to take a step back, look at all of the information that was available, and to see whether or not there was either relatively conclusive information or perhaps some suggestion of information that was not conclusive either way.

I think the category of limited or suggestive is really very much what it says in the title. It is suggestive. There is some information there that looks as though, as was commented by the other investigators, it might be interesting. I think they took an absolutely proper stance when they published their data, which is to be cautious, to look very critically at the information, and to be careful about its limitations.

Our job was somewhat different, to take, again, a step back and look at all of the information together, and it did appear that there was enough information out there to put it in this suggestive category. I think what that means to me is that additional scientific information as it becomes available may potentially raise conditions that are in that category up into a higher category of sufficient evidence or equally well could lower it into a category of less available data or even potentially no association.

So I think, again, there is a suggestion that there is something there, but I would echo what the other committee members have said, that this is not conclusive. It does not imply causality. It is just, based on all of the evidence, the statistics suggest that there is something of interest, and it should be pursued further.

Mr. HUTCHINSON. Let me address this question to any of the panel members who would like to respond to it.

Recognizing the importance of maternal health, and I think, Dr. Erickson, you referred to that, two April 10 articles in the Journal of the American Medical Association concluded that obese women are twice as likely to have children with neural tube defects, such as spina bifida.

I understand that folic acid is a big issue also in the effect upon spina bifida. Would those kinds of considerations, obesity in material health or the lack of folic acid, would they have any effect upon the recent findings of the Institute's update and how spina bifida was classified?

To anyone who would like to respond to that. If no one responds, then I have to tell somebody.

Dr. ERICKSON. I will be happy to respond, Mr. Hutchinson, although not relative to the Institute of Medicine classification, but in general, let me say these two reports are just brand new, and I have not had time to review them in great detail. These are the two reports from the Journal of the American Medical Association last week.

But they do seem to indicate that maternal overweight is a substantive risk factor for having a fetus affected with spina bifida or anencephaly, and as I pointed out in my testimony, we now know that folic acid is an important preventive substance.

One of the reasons for being cautious about the findings relative to paternal effects and, in particular, with Vietnam veterans is the very small numbers of adverse outcomes that have been involved in the studies. In general, the control group should take care of things like that. There should be as many babies born with neural tube defects, anencephaly and spina bifida, due to, let's say, a lack of folic acid in the mothers in the Vietnam group as in the comparison group. So that should sort of all wash out in the end.

But when a small number are involved, one or two cases could tip the scale dramatically, and that is the basic reason for being cautious, especially when there are small numbers of cases.

Mr. HUTCHINSON. With this new information or with the articles that have been published regarding obesity and its effect, is there a way to go back to the Vietnam studies and to see whether that may have been a factor in those cases of spina bifida that might have impacted? I mean apparently all of this study was basically going back and looking at statistical aberrations from the norm. I am wondering if those kinds of factors can be somehow recomputed with this new information.

Dr. ERICKSON. I can only speak for the CDC study. In the Vietnam experience study, I think that would be very difficult. It would require the obtaining new information from the individuals who participated in the study.

In the CDC birth defects study based in Atlanta, it would be possible, and I can make a commitment to do that. One of my colleagues is at this moment working on the issue of maternal obesity and the risk for neural tube defects. I think it would be relatively simple for us to check out the possible connection with service in Vietnam among the fathers of these babies.

Dr. MICHALEK. Mr. Chairman, with regard to the Air Force study, we do have the necessary records, I believe.

Mr. HUTCHINSON. Colonel Henriksen, do you have a comment?

Col. HENRIKSEN. Yes. We have already discussed going back and seeing if we could retrieve that data, but, again, the difficult we will have is our total number of cases are small, three cases, and you would need to see a huge difference in the maternal groups in terms of either obesity or folic acid to bias it enough to account for the differential.

So we will still have sparse data even after we determine that, but we will look at it, and if we can, we certainly will, but the numbers are still small.

Mr. HUTCHINSON. Mr. Edwards.

Mr. EDWARDS. Thank you, Mr. Chairman.

I just want to follow up on the one question that the Chairman asked you, Dr. Tollerud, in regard to definition of sufficient, limited, suggestive, or inadequate associations.

Can you put any sort of statistical probability on those definitions? Are they based on a statistical probability?

It has been a while since I have taken statistics, but I know normally you are talking about standard deviations and mathematical probabilities, there being a relationship or an association between cause and effect, and I know that those probabilities do not prove or disprove the scientific cause-effect, but at least it gives you some suggestion.

Can we take it out of generic statements and put it into any kind of mathematical probability of what you mean when you say sufficient or limited or inadequate association?

Dr. TOLLERUD. Yes. It is an excellent question, and it is an important question. I was on the original committee that set up these categories and that generated the first report. We spent a great deal of time in discussing what the categories meant among the committee members and actually struggled. We have a number of

committee members who have really extensive expertise in biostatistics and epidemiology and really struggled with trying to put some bounds, some more specific bounds, because we recognized that questions like these were going to arise not only from you all in committees within the government, but certainly others.

From those extensive discussions, we were not able to apply any kind of rigorous numerical system to those categories. They really are categories that are based on stepping back. They individually, as the investigators have said, took the rigorous scientific approach, and in fact, that is how we selected the important studies that we did on which to weigh the evidence, but within the categories themselves, it is really not possible to be more precise.

Mr. EDWARDS. Very good. Thank you.

Thank you, Mr. Chairman.

Mr. HUTCHINSON. Mr. Tejeda.

Mr. TEJEDA. Did any of you serve in Vietnam?

Dr. TOLLERUD. No.

Dr. MICHALEK. No, sir.

Mr. TEJEDA. It is my understanding that Agent Orange was started or began being used or dropped in Vietnam. Do you k now what year?

Dr. MICHALEK. 1961.

Mr. TEJEDA. Yes, 1961, 1962. That is correct. As you know, we got many of our troops in there in 1965. Of course, we had troops there before, but basically advisors, et cetera. Many of our battalions and regiments and divisions started in 1965.

Let me just ask this question. What if Agent Orange was dropped on different jungle areas, different village areas, different rice paddies in Vietnam? How long would that last?

What if someone came in there a year later? What if this Agent Orange went into that rice paddy? What if those leaves were dropped, and that is why they did it, so that people could not hide or so that people could be seen? How long would that last.

Or what if the leaves that grew back, if they grow back, what if a Vietnam veteran, a Marine, an Army or a Seal, climbed that tree or jumped behind that tree to be saved or was walking or patrolling the rice paddy and began being fired on and had to come down and some water got in his eye, up his nose, in his mouth accidentally, in his ear?

Have you all studied that or have you all seen that? Dr. Tollerud, Dr. Olshan, Dr. Erickson, any one of you, have you all studied that? Have you all seen that?

Dr. MICHALEK. I do not know about that. It is degraded by sunlight.

Can you all add anything to that?

Dr. TOLLERUD. I do not know. The focus of the Committee was really on the health effects. I believe the chapter on toxicology in the original report may, in fact, speak to that, but I do not have that information at my fingertips.

Mr. TEJEDA. Let me ask. Do you know or have you studied how many veterans who served in Vietnam have passed away since they returned from Vietnam that perhaps you did not get the chance to speak with, to study, or to do exams on?

As a matter of fact, when did you all start this exam? When did you all start this study? Yes, sir.

Dr. MICHALEK. Sir, the protocol for this study was developed in 1977.

Mr. TEJEDA. Okay.

Dr. MICHALEK. Reviewed by the National Academy of Sciences in 1978. The study began in 1982.

I do have some information to give you, in fact, in this regard. Prior to giving the dioxin results to our study subjects, we administered a questionnaire to our Ranch Hand ground crew, which constituted about 75 percent of the Ranch Hand group, the enlisted ground crew. We asked them about days of skin exposure to dioxin when they were in Vietnam. We asked them about using herbicide as a hand cleaner, about wearing herbicide soaked clothing, and on the basis of that questionnaire, we are able to simply count the number of days of reported skin exposure in Vietnam.

And later we were able to relate that information with their actual dioxin body burden, and we did find a correlation, and that was recently published in 1995. So I think that is the first evidence of a direct relationship between day's dioxin body burden and what actually happened in Vietnam to our Ranch Hand enlisted personnel.

Mr. TEJEDA. Do you know when the Agent Orange was stopped being used in Vietnam?

Dr. MICHALEK. I believe it was 1971.

Mr. TEJEDA. 1970. That is correct.

Dr. MICHALEK. 1970.

Mr. TEJEDA. I am very concerned because it has been brought to my attention that there were some veterans who served there who, of course, have not been looked at or examined or studied, and they may have different things to say. You know there were hundreds of thousands who did serve there. Many may not have come into that situation, but many may have.

And I am just very, very concerned about that, and of course, you mentioned that the study was begun in 1977, and this of course was stopped in 1970, but many served in there since 1962. We got the majority of our troops in there in 1965 and began moving forward from there.

So I am very concerned, and I certainly want to hear from you just exactly what you have done. If that remained in water or in animals or how long did that stay in some of those trees or could leaves grow back? Have you studied that? Have you looked at that?

Have you visited Vietnam to study that?

Dr. MICHALEK. No, I have not revisited Vietnam. The NAS included a careful review of the environmental fate of dioxin in their first report. They reviewed many animal and human studies in that regard. I cannot recite those myself right now.

Mr. TEJEDA. Do you know how many Vietnam veterans have passed away because of something they may have come in contact with in Vietnam?

Dr. TOLLERUD. No, I don't have access to this specific information. I am sure the Department of Veterans Affairs would be better able to answer those questions.

Mr. TEJEDA. Right. Of course, I am not talking about those who were killed there in action. I am talking about someone who may come in contact or who may have come in contact with Agent Orange, and then who knows what may have happened later?

Dr. TOLLERUD. Sure, but what I can say is that as the Committee held its deliberations, both the initial committee and the subsequent committee, we attempted to get at the issues that you're asking. In fact, each of the Committees have held open forums, particularly targeting veterans' organizations, but also to the general public, to the media, to congressional leaders and those kinds of things, to try to elicit that kind of information, and I think each of the committee members were very impressed with the kind of testimony, some of which was by survivors, some of which was by brothers, by spouses, by children of Vietnam veterans who had passed away. So there was an explicit attempt to gather that kind of information.

The second, I think, is that on a reassuring note, there is a great deal of scientific interest in the questions you are asking about the Vietnam theater, about the environmental fate of dioxin and the herbicides and, in fact, what might have happened to veterans and civilians who were exposed for longer time periods in Vietnam.

We have had discussions with those investigators. They have given testimony at our committee meetings. I am aware that a number of those investigators have themselves made trips to Vietnam. So I think that is an area of active scientific debate and discussion which will result in new information coming to the fore, which can then be evaluated.

Mr. TEJEDA. Okay. Well, I am very concerned. I knew people who served there, and I have tried to get hold of them, and a couple of them had passed away. Now, what they passed away from I do not know if it dealt with maybe something they came in contact with in Vietnam or something else. I do not know, but I am certainly very concerned.

I served in Vietnam. I was wounded in Vietnam, and I am just very concerned if you all have come in contact or tried to bring in perhaps some doctors or others who served in Vietnam.

Anyhow, thank you very much, Mr. Chairman.

Mr. HUTCHINSON. Thank you, Mr. Tejeda.

Before you arrived, I think in my statement we paid special tribute and thanks to the members of the full committee who served during Vietnam, including yourself, and we certainly appreciate your service there.

It is my understanding there was a registry established in the 1980s regarding those who felt they were exposed, and it might be a question we want to follow up with the VA as to what the outcome of that was. Mr. Gutierrez.

Mr. GUTIERREZ. Thank you, Mr. Chairman.

Let me see if I understand some of the different testimony. Someone said something about exposure and health outcome, and they said that you get spina bifida, and you find it in five in 10,000 in the general population; is that correct?

And that in the Ranch Hand study it was three out of how many?

Dr. MICHALEK. Three out of 500.

Mr. GUTIERREZ. Three out of 500, and it is five out 10,000 in the general population, and in the other studies, what were the numbers? Anybody. In the Ranch Hand study it was three out of 500. The other studies?

Dr. ERICKSON. Oh, roughly in the range of one in 1,000.

Mr. GUTIERREZ. One in 1,000?

Dr. ERICKSON. Yes.

Mr. GUTIERREZ. And so the only study that showed any large number was the Ranch Hand study?

Dr. MICHALEK. Well, in terms of proportions, yes. That is the conclusion. The Ranch Hand proportion was greater. That is true.

Mr. KENNEDY. Would the gentleman yield just briefly?

Mr. GUTIERREZ. Sure.

Mr. KENNEDY. Dr. Tollerud, didn't you mention the statistics of four out of 792 in your testimony?

Dr. TOLLERUD. I will yield to the Ranch Hand. The numbers that I gave were general numbers of live births in the group and the four related to neural tube defects. Perhaps you can give the more specifics.

Dr. MICHALEK. I think we are talking spina bifida, and when I mentioned three, we are talking about spina bifida. Then the issue is what denominator do we use. If we use all Ranch Handers, the denominator is 792. If we use only those Ranch Handers who have dioxin levels above background levels, that denominator is about 500.

Mr. KENNEDY. Thank you.

Excuse me.

Mr. GUTIERREZ. Sure.

So you then say that it is limited or suggestive evidence in terms of spina bifida, Dr. Tollerud? Is that what we come up with?

Dr. TOLLERUD. Right.

Mr. GUTIERREZ. On the basis of three out of 500?

Dr. TOLLERUD. I think what has been alluded to in, I think, each of both the investigators and the committee members have made the same kinds of statements, and that is that when you deal with statistics and you have very small numbers of observations, one number going one way or another way can dramatically change your interpretation of the data. You just have to be very, very cautious when dealing with small numbers.

Birth defects occur. When you look at specific birth defects, they are unusual events. They occur with very low frequency. Therefore, they require large populations.

I think most of us, if I put on my hat as an investigator, as an epidemiologist, if somebody came to me and said you would like to study this birth defect, spina bifida, and the rate is five per 10,000; how many subjects do you want to study in your exposure group and your control group? I mean I am talking many thousands to be confident so that when the numbers come back I know what they mean.

We had numerous experts on the Committee of epidemiologists and biostatisticians, and all I can say is that when you take a step back and you look at all of the information that was there, it falls into that category that, yes, there is some suggestion, but it is far

from conclusive, and the link with causality is very far from being made.

Mr. GUTIERREZ. And obviously we have to rate these issues because now the way I understand the way the law works, the task force at VA is going to take your information, and you put it into a limited or suggestive evidence, and someone said, "Well, maybe we need to come back in a couple of years and continue to look at this issue." But the problem is we will not do anything about it at the VA, and I think someone suggested it could go to inadequate or insufficient evidence or you could take it up a tier to sufficient evidence, which may make a difference obviously in the veteran's life and their life with their child.

So I think it is a rather critical issue to raise it, and then how do we get to some sufficient? Because in the past, it is my understanding that the VA has compensated illnesses, diseases that have been classified as limited or suggestive evidence, and of course, with prostate cancer they have not.

So as you see it, when the next panel comes up, they are going to be relying on your information. We are going to be relying on both of these information in order to make decisions about where we should go.

Now, in terms of in the 1993 study, I believe it was found that respiratory cancer, prostate cancer, and multiple myeloma were found in the limited or suggestive evidence, and that that was found once again in your study. Can anybody talk to that issue?

Dr. TOLLERUD. Right, there was no change. Essentially for each of these disease outcomes, the primary focus of this new committee was on information that has come to light in the ensuing 2 years, but in evaluating these, we did go back and add that new information to the old information. We did not discard anything that had been going on in the past, and essentially for those diseases, there was not enough new information to warrant a change in category, according to the Committee's judgment.

Mr. GUTIERREZ. Okay. So you reevaluated the information in the 1995 study and concurred with designating as limited or suggestive evidence in terms of respiratory cancer, prostate cancer, and multiple myeloma once again?

Dr. TOLLERUD. Correct.

Mr. GUTIERREZ. And you kept it at the same category.

Dr. TOLLERUD. Correct.

Mr. GUTIERREZ. Which is what could happen with spina bifida and the information that you found today that we just will not know. We will just leave it because limited or suggestive evidence is not a weak category, right? It is not something that we should just discard. I mean you have four categories, right?

Dr. TOLLERUD. Right.

Mr. GUTIERREZ. It is Category 2, and I think the word kind of says it, limited or suggestive evidence. So what would you do? What do you think we should do?

Dr. TOLLERUD. Well, I think the original law mandated a review of some form every 2 years. I think that can potentially take different forms. It might be a literature review as was done this time, with literature that has been published.

On the other hand, there has been some discussion of a more proactive view of bringing investigators together in a workshop format where we could actually perhaps stimulate some re-analysis of these large, large databases that are out there.

Every year computers improve. Modeling programs improve. It has already been alluded to the individual investigators here have at their disposal powerful, new techniques now that were not available a decade ago or even 5 years ago. So I think there is some potential that, in fact, new information can be brought to light by bringing together investigators in a structured format.

Mr. GUTIERREZ. In other words, you do not want to answer the question about what we should do because since you are all doctors and health care professionals, I think you should probably have a professional recommendation. You know, what do you do with? You know, you as a doctor or as doctors, all of you, what would you do with limited or suggestive evidence in terms of treating the population? Would you go out there and say, "God, you know, I think we have a problem here. We should go out there and treat it and begin to give the Vitamin D, you know, and start acting on this issue," or as doctors we are just going to give the VA the information and say, "Well, that is all"?

Dr. TOLLERUD. You are asking what I think is a policy decision, and that is a decision that is outside of the purview of the Committee.

Mr. GUTIERREZ. But you guys are doctors.

Mr. HUTCHINSON. Mr. Gutierrez, we are going to have another round. Mr. Kennedy.

Mr. KENNEDY. Thank you very much, Mr. Chairman.

It sounds to me as though we are sort of trying to deal with almost two different standards. One is sort of a cause and effect standard that I think when we are trying to achieve a direct link or direct evidence based on some statistical analysis, it is going to be very difficult to prove almost anything in life, although obviously there are going to be some that fit within that category.

My understanding is that the Agent Orange Act that this committee and the Congress adopted did not, in fact, hold you to the standard of cause and effect, but rather that there be credible evidence of statistical association.

So I think going back to Mr. Tejeda's argument, I think he is basically getting at, and he wrote me a note here saying do you know how many veterans have died as a result of Agent Orange? And I said, "Well, listen, Frank. The trouble is that under the evidence rules that you guys are trying to utilize, the answer is going to be, no, you do not know." Right?

The question is whether or not there is credible evidence for a statistical association between four in 792 or three in 500 or five in 10,000 that would lead you to believe that there is some relationship. You, Dr. Tollerud, who were sort of responsible for reviewing all of these different statistics, came back and said, "Well, there appears that there is, in fact, what I would consider in listening to you credible evidence of a statistical association." But then you couched it when you were before the committee in your testimony saying, "But the statistical association really require that we

study it further, and if we study it further, it might come out either way."

Is that correct? Is that what you are saying to us?

Dr. TOLLERUD. Yes.

Mr. KENNEDY. I would think that we are really dealing with a situation that is similar to the Gulf War Syndrome, where these veterans and the children of these veterans are looking to their government to give them some assurance that their service to this country has some relationship toward this anomaly, which in fact means that their health or their children's health is not as good as the rest of the population.

Given what you have uncovered thus far, my question to you is: do you believe that there is credible evidence of a statistical association, not cause and effect, but a statistical association between exposures to Agent Orange and the kinds of illnesses, and it does not have to be spina bifida; it can go on to the other illnesses, Hodgkin's, non-Hodgkin's lymphoma or whatever else it was? Gosh, it was some terrible list. Spina bifida and the peripheral neuropathy.

Dr. TOLLERUD. Neuropathy, right.

Mr. KENNEDY. Neuropathy. Thank you.

Can you answer just right down the line, please?

Dr. TOLLERUD. You raised a number of very important points. First of all, your latest point about whether there is credible evidence. The published scientific literature in the nature of peer review, how important studies like the CDC studies and the Ranch Hand study get into the literature, that can be credible evidence in favor of an association or credible evidence not in favor of an association.

Mr. KENNEDY. I know. So I am asking you is it credible evidence in favor.

Dr. TOLLERUD. It falls squarely in the category that there is limited and suggestive evidence. Credible is not in our—

Mr. KENNEDY. You have come up with a new category.

Dr. TOLLERUD. No. Credible is not in our category definitions.

Mr. HUTCHINSON. Mr. Kennedy, while I will let you continue, I just want the members to be apprised we have got about 5 minutes on this vote.

You may continue if you wish.

Mr. KENNEDY. Thank you, Mr. Chairman, and if you want to scoot, that is fine, too. I will run over.

Anyway, is there, in fact, a category that you just described? What was the category?

Dr. TOLLERUD. Limited or suggestive evidence category is Category 2.

Mr. KENNEDY. And so you would say there is limited or suggested?

Dr. TOLLERUD. Correct.

Mr. KENNEDY. Would you, Dr. Olshan?

Dr. OLSHAN. Yes, I would say there is limited suggestive evidence for statistical association.

Mr. KENNEDY. Dr. Erickson?

Dr. ERICKSON. I am not comfortable with those particular terms. They are not terms I would have chosen. They are the panel's

terms, but I think that is perhaps not a bad description in some ways of the situation.

Mr. KENNEDY. Dr. Michalek?

Dr. MICHALEK. I think unusual might be a better word. I want to warn you that when you are talking about making a decision based on one, two, or three numbers of cases, you are working in an area where when we assess birth defects again in another year, when our study subjects come back, it could happen, for example that, say, two controls have children with birth defects.

Mr. KENNEDY. Fine.

Dr. MICHALEK. And then the issue is gone.

Mr. KENNEDY. We have got to scoot. So I am sorry, Doctor. We have got to make this short. Colonel.

Col. HENRIKSEN. Sir, the numbers are simply too small to have a good opinion. I wish it were different, but that is a fact.

Mr. KENNEDY. Thank you. Thank you very much.

Mr. HUTCHINSON. The subcommittee will stand in recess for 15 minutes, and we beg the panel's indulgence. We will go vote and get back as quick as we can.

[Recess.]

Mr. HUTCHINSON. We will go ahead and get started.

They are having a little ceremony on the floor welcoming a new member. Mr. Edwards asked us to go ahead. He is going to return as soon as he can.

I would like to recognize at this time a member of the full committee and someone who has been very involved in the Agent Orange issue, Mr. Lane Evans.

Mr. EVANS. Thank you, Mr. Chairman.

I guess I would like to ask just a few questions, having not heard Congressman Kennedy's questions and answers, but just to make it very clear, maybe this is more of a statement than a question.

This Congress long ago established that science may not be able to actually prove cause and effect relationships between herbicide exposure and disease in human beings, and I understand Congressman Kennedy got into what limited and suggestive evidence is and what that amounts to in terms of our standards.

Evidence being suggestive of a causation is helpful to this committee. As I understand it though, the term "limitation" refers to limitations of the studies themselves, not of the evidence that might have been ascertained; is that correct?

In other words, when we speak about limited evidence, or suggestive and limited evidence, the term "limited" really refers to potential problems in the studies themselves, not the probative value of the evidence that we have been able to gather; is that correct?

Dr. TOLLERUD. I guess I have some difficulty in distinguishing between those two because the evidence is based on the qualities of the study and the limitations in the study itself. I guess I would probably state it that the evidence for a statistical association is, in fact, itself limited. It is suggestive of an association, but is limited by the nature of the studies themselves.

So I am not sure it is possible to disentangle those two concepts completely.

Mr. EVANS. Has anything been discussed about going to Vietnam and working with their 1080 committee and Dr. Schechter of the University of New York to gather more information?

I have been there myself and met with the 1080 committee at the university there. I also talked to Dr. Schechter, who has testified here. Is there any possibility now that we have a better relationship with that country that that might be useful to us?

Dr. TOLLERUD. I think potentially. Several of the committee members had communications with Dr. Schechter before one of his recent committee trips to Vietnam. We had invited him to present any of that information and other participants of that committee bring any of that information to the fore.

I think that will be the subject of future scientific investigation. The Committee itself, the way it was constituted and the charge to the IOM was to evaluate published literature, and at this point I think the thing like field trips to Vietnam and beginning investigations in Vietnam itself are currently outside of that purview.

But I do think it is of interest. I think the committee members agreed, in general, that studies, potentially studies of civilians exposed to herbicides, Agent Orange, and dioxin are important in other countries, as well as in the United States.

Mr. EVANS. My colleague, Frank Tejeda, asked about how long dioxin remained toxic, I guess, when it was sprayed in jungle areas or rice paddies, but it is very clear, isn't it, that dioxin that is absorbed is a very highly toxic substance that stays in the body for many years, including decades?

Dr. TOLLERUD. Right. Maybe the CDC representatives could discuss the specifics of the half-life in the body, but in general, your statement is correct.

Dr. MICHALEK. Yes, sir. The latest estimate is about 8.7 years' half-life, but we find that the half-life changes with body fat history and that heavier people tend to retain the dioxin longer in their bodies.

Mr. EVANS. I am jumping around, but over what period of time will a child in the family, a child with spina bifida, have to deal with the disabling effects of that illness?

Dr. ERICKSON. Lifetime.

Mr. EVANS. I am sorry?

Dr. ERICKSON. Lifetime.

Mr. EVANS. And quite often involving very expensive and risky surgeries throughout the lifetime of that child?

Dr. ERICKSON. Yes. A recent estimate based on data from the State of California is that the lifetime medical costs are at least $250,000, medical costs alone. Children with spina bifida by the time they reach the age of six will have, on average, had six major surgeries.

Mr. EVANS. Including one maybe just a few days after they are born?

Dr. ERICKSON. Yes.

Mr. EVANS. All right. Mr. Chairman, thank you for your indulgence. I appreciate it.

Mr. HUTCHINSON. Thank you, Lane.

Before I go to Chris, if I could, Dr. Erickson, I think when Mr. Kennedy was kind of polling the panel regarding their position on

the limited association of the evidence—I want to get the exact words—that you joined Dr. Olshan and Dr. Tollerud in saying with some reservations that there was, in fact.

That is a change of position from when you did your report on the Atlanta study on Agent Orange in which you concluded that there was no evidence in favor of the position that veterans, in particular, Vietnam veterans, have a different risk for fathering babies with birth defects.

So what the Committee did has changed your opinion on that?

Dr. ERICKSON. I would say the appearance of the Ranch Hand data has changed my opinion a little bit, but I believe that the data are still very, very limited, subject to potential biases of one sort and another that could have influenced these results.

Mr. HUTCHINSON. Mr. Smith, are you prepared for questioning yet? Would you like a moment?

Mr. SMITH. Thank you, Mr. Chairman. I do have some questions I would like to submit for the record.

Dr. Michalek, understanding your interest and familiarity with the Ranch Hand study, could you provide the committee an assessment of the general health status of the Ranch Hand veterans? And could you describe their overall general health? What has been the most frequent cause of death? What has been their experience with malignant neoplasms, and are these veterans more likely to have liver problems or higher mortality due to diseases of the liver?

Dr. MICHALEK. First, I would like to respond to those questions in writing later in detail. Is that permissible?

Mr. SMITH. That would be fine.

Dr. MICHALEK. All right. However, I would like to give you a quick overview of those areas.

With regard to mortality, they are dying as a group of pretty much the same causes as the control group. I think our most common cause of death is accidents actually.

Their rate of death with respect to cancer is actually less than the control group. The relative risk is about 80 percent.

We are finding an increased risk of cardiovascular related deaths in our enlisted ground crew, which we have noticed now for the last several years and which we are now studying very carefully, to pull medical records on the deceased to look for evidence of cardiovascular conditions.

On the general health of the individuals, we are finding actually less cancer in the living Ranch Handers than in the control group, and that is being written up in an article right now. With respect to prostate, for example, the Ranch Handers are having less prostate cancer than the controls.

The overall experience of the Ranch Handers with respect to cancer is less than the controls. We are seeing no particular type of cancer in the Ranch Hand group that is elevated.

We are seeing suggestive effects in immunology, which are arguable. There is no clear pattern there that we have been able to identify as a detriment. However, some of the effects are, we consider, important enough to continue studying.

We see endocrine effects that are statistically clearly related to dioxin body burden, but which are lacking of biological mechanism at this point, and so we are beginning collaboration with toxi-

cologists at the University of California to study that issue further, to try to understand the mechanism.

We are seeing overall general health of the two groups nearly equivalent. Although we see increased evidence of heart disease related deaths in the enlisted ground crew, paradoxically, we see little evidence of a group difference on physical examination. So that just muddies the picture and makes the data more difficult to understand.

All of these issues will be, of course, studied again at our next physical in 1997, and many of the issues I have just described are either published or in press right now in research papers.

Mr. SMITH. Thank you, Doctor, and I look forward to your expanded answer to that question, and I do thank you for that answer.

Dr. Erickson, as you pointed out in your testimony, and I apologize, Mr. Chairman, for being late. I was at another committee hearing that precluded my being here, but in reading your testimony, you point out that although we have been unable to provide definitive answers about Vietnam veterans' risks for fathering babies with spina bifida, the studies conducted have contributed to a discovery of a tremendous prevention opportunity.

Could you elaborate as to what the VA can and should be doing to assure that those veterans who have been affected by Agent Orange know what they can do to mitigate the possibility of spina bifida.

Dr. ERICKSON. Well, the Public Health Service has made the recommendation that all women of reproductive age in the United States should consume 400 micrograms of folic acid each day. That is the amount that is in a typical multivitamin pill, and we would hope that some day in this country all women would follow that, including women whose mates were Vietnam veterans.

Mr. SMITH. But is there anything specific that the subgroup of population, that is to say, Vietnam veterans—is there a way to make them aware using the channels at your disposal, the VA's disposal, since so many have been identified as being at risk of some kind of anomalies attributable to Agent Orange?

Dr. ERICKSON. I do not feel qualified to answer. I do not know what channels the VA has to the veterans.

Mr. SMITH. Okay. That would be a question that we could pose to VA later on.

But in your view, the Public Health Service may make a recommendation, but we all know that that does not necessarily translate to getting to the eyes and ears of the people who need to hear it.

Dr. ERICKSON. Right, right.

Mr. SMITH. Do you think that would be a good idea, if the VA undertook an education effort?

Dr. ERICKSON. I think it would be a good idea if we could have a concerted effort to reach all women in this country, including women whose mates are Vietnam veterans.

Mr. SMITH. Dr. Tollerud, although the Institute of Medicine generally found that it was not possible to quantify the degree of risk in Vietnam veterans from exposure to herbicides, this view was not

shared by two committee members. Could you summarize their point of view?

Dr. TOLLERUD. I am not sure that that is an accurate statement, that that view is not shared by the committee members. There were two committee members how were really experts in mathematical modeling and estimating exposures and such, who proposed a formula which could be used to estimate exposure levels of groups of veterans, and frankly, the model, if you read the appendix, is very complicated. There were a number of detailed mathematical, technical issues about what elements could be put into that model, what assumptions needed to be made for the model, and there simply was not enough time in the committee process to really work through all of those issues to where the Committee could come to a consensus view.

It was felt to be important information, sufficiently important that it warranted inclusion in the report as an appendix, but it is included as an appendix by those two individuals, and just as a follow-on to that, I think it should not be interpreted as those committee members disagreeing with the Committee in terms of the body of the report.

The report itself is a consensus document with unanimous consensus, including those two committee members, on all of the findings that are contained in the body of the report. So I think it was really more of a technical modeling issue, and I think some additional light will be shed on that with the IOM's current activity of exposure assessment modeling.

Mr. SMITH. I thank you for that clarification.

I yield back.

Mr. HUTCHINSON. Thank you, Mr. Smith.

Now, if I am correct, I keep going back to Mr. Kennedy's little survey. We have a shift over the last 12 years in the opinion of Dr. Erickson, but, Dr. Michalek, in your article that was published in January 1995, you state that data provided little or no support for the theory that paternal exposure to dioxin is associated with adverse reproductive outcomes after service in Southeast Asia.

Have you changed your opinion any with the IOM report?

Dr. MICHALEK. No, I do not think we have. We recognize that the data we saw in the nervous system anomalies, well, that was the reason for the term "little." We view that, as epidemiologists, as weak. We see that it is consistent with other studies, namely, the VES and CDC birth defect study. That is as far as we are able to go because those co-authors who are experts in teratology and birth defects were unable to hypothesize even a mechanism to explain what we are seeing.

So that what we see is a combination of a suggestive statistical pattern with an absence of a biological mechanism. That qualifies as almost the weakest form of evidence in this area of research.

We acknowledge that in our paper, and I believe that is what is reflected in the Institute of Medicine report in different language.

Mr. HUTCHINSON. If you had been on the Committee, would you have placed this in the limited suggestive evidence of an association category?

Dr. MICHALEK. As a statistician, I would have to say, yes, because of the consistency of the three studies, but I think that is as far as we are able to go in describing the results.

Mr. HUTCHINSON. What does it take, and I will address this to the entire panel, what does it take to move it from limited suggestive evidence of association to sufficient evidence of an association? What kind of data would you have to have?

Dr. TOLLERUD. I can begin a response to that. I do not think that can be quantified. What we saw in the last committee report was there were—

Mr. HUTCHINSON. That might not be satisfying to those veterans.

Dr. TOLLERUD. I understand, and I expect that it is not satisfying to the veterans. It is one of the difficult areas that we have dealt with, and I wish it could be better quantified.

Between the 1993 report and the current report, there were a couple of diseases which changed category. One was actually moved out of the sufficient category into the limited suggestive because of new carefully done epidemiologic studies looking at a relationship, which in the past was proposed based on other kinds of data, particularly toxicological data.

So I think it is difficult to predict which way things will go, and I would say it is virtually impossible to come up with any kind of quantitation that would say what it would take to move it up any more than I could say what would it take to move it down a category.

Mr. HUTCHINSON. The four categories, are they somewhat subjective? Those are not really scientific categories, or are they? Is there a level of subjectivity in how those are interpreted?

Dr. TOLLERUD. There is a level of judgment that is involved in placing those conditions into the categories, and part of the committee structure involved a lot of discussion and debate, hearing from experts in different areas and arriving at a consensus. So, yes, I would say whether you call it subjective or judgment, these are not clearly, crisply defined categories that make it easy to draw a distinction between—

Mr. HUTCHINSON. Would the other panel members care to comment on that categorization?

Dr. OLSHAN. I would just like to say that the categories of evidence we used are similar, not exactly the same, but similar to the categories used by the International Agency for Research on Cancer when they make judgments about the carcinogenicity of various agents. So it is somewhat similar to their categories.

Mr. HUTCHINSON. Anybody else?

Dr. MICHALEK. I have nothing further to add.

Mr. HUTCHINSON. Just as a layman looking at the general population, five out of 10,000 births being spina bifida and in the Ranch Hand study three out of 500, I mean on the surface there is a statistical aberration, even though acknowledged, and that is what I tried to bring up earlier, there could be a lot of different factors, I guess. I understand everybody saying there was a need for more research and more data.

But in 1976, there was a serious chemical accident that contaminated a large area known as Seveso near Milan, Italy. Over 31,000 inhabitants in the area were exposed to dioxin, including women

and children. There was a subsequent study that was conducted in regards to those 31,000 inhabitants, the population residing in that area, over a 5-year period by the Italian government, including the monitoring of birth defects.

My understanding is that that study found that there was not any malformation births, no deviation from the norm in the very large number that were studied. Could any of you comment on that in relationship to the IOM report?

Dr. OLSHAN. We did consider the Seveso report, and we always are interested in the results of the Seveso accident studies. I do not remember the exact number of pregnancies. You are correct that there was no statistical association reported.

However, as I remember, the number of pregnancies that were actually part of the study was relatively small, and that they probably could only say anything about all types of birth defects combined. So I think here, again, is an issue of numbers.

So basically we did not find an association, but we had some concern about how many pregnancies were actually part of this study.

Dr. TOLLERUD. The other aspect, I think, that is important to note about population studies like the Seveso study, if you look at the extraordinary resources and talent at the CDC and in the Air Force Ranch Hand study, you could talk about the number of individuals that are involved in this kind of a study. The years that it takes even in an extremely well defined, highly motivated, very compliant population of enlisted folks who are interested in the outcomes, even in that group it is extraordinarily difficult to collect the kind of information that is necessary to make concrete judgments.

When you deal with the general population, many of whom moved out of the area, frankly, right after the operation, information is much more difficult to obtain, and that 31,000 number really does not reflect a very stable study population.

Mr. HUTCHINSON. We have been joined by a couple of members who did not have an opportunity on the first round. So Mr. Bishop.

OPENING STATEMENT OF HON. SANFORD BISHOP

Mr. BISHOP. Thank you very much, Mr. Chairman.

Let me just say that I appreciate the integrity with which the studies have been done, and I appreciate the desire to be as cautious as possible in reaching conclusions.

However, I do have some concern that all of the caution could possibly and will, in fact, result in delay, and delay for many of the people who may be the subject of the studies, but who more importantly may be the victims means that the quality of their lives will be diminished and that the length of some of their lives may, in fact, be diminished. To what extent we do not know.

But let me just ask if I am correct in reviewing the testimony that the Committee found. Am I correct in understanding that there was a finding of sufficient evidence of a statistical association between exposure to herbicides or dioxin and three different kinds of cancer, soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease, and that there was sufficient evidence of an association with chloracne, which is a skin condition? Is that correct?

Dr. TOLLERUD. Correct.

Mr. BISHOP. You found that there was limited suggestive evidence of an association between exposure to herbicides or dioxin and three other types of cancers, respiratory cancers, prostate cancer, and multiple myeloma; is that correct?

Dr. TOLLERUD. Correct.

Mr. BISHOP. And that there were two new health effects in the category of limited or suggestive evidence of an association between herbicide or dioxin exposure, which is an acute transient form of peripheral neuropathy, a nerve disorder that can lead to pain, numbness, and weakness of the limbs.

Dr. TOLLERUD. That was found.

Mr. BISHOP. Then you get down to the spina bifida, which is the limited or suggestive evidence, that it may be associated with the spina bifida birth defect.

Does this not suggest in and of itself that there is reason for us to have serious concern and that we who are charged with the public trust of responsibility to protect veterans and their families ought to be able to go with this information and to do something to try to relieve the suffering by at least approving some kinds of ameliorative, some kind of remedial efforts to try to make these folks whole or at least compensate them?

But we have got to depend on your kind of discipline to give us the information, and I think my colleague, Mr. Gutierrez, has asked you earlier. You are doctors; you are professionals. We have to take your professional advice, but doesn't this give us cause to do something rather than do nothing, rather than just wait?

Can I just ask you to respond to that?

Dr. TOLLERUD. I will start it out. I think others may wish to respond.

You are the experts in the legislative area.

Mr. BISHOP. Oh, no, we are not experts. We are the policy makers.

Dr. TOLLERUD. I understand.

Mr. BISHOP. And we depend on you for the facts.

Dr. TOLLERUD. What we have tried to do in the Committee is to present the evidence and the strength or weakness of the evidence in as precise, clear way as possible to allow you all to do what you need to do on the policy front. There are limitations to science. There are limitations to the statistics, and we can simply provide you with the information, and then you need to deal with it.

Someone asked the question: what do you do as a doctor? What I do as a physician when I have a patient in my office is very different from what I do sitting on a committee and looking at statistical associations. When someone comes into my office, they are not a statistic. They are a person. They are my patient. I deal with them one on one. I take all of the information that is out there and is available, and I take care of them.

That is a very, very different process. That is an individual process.

Mr. BISHOP. Can I interrupt you for a moment?

Dr. TOLLERUD. Certainly.

Mr. BISHOP. If you would allow me to, we are charged with the responsibility to look after those that are our constituents. When

they come to see us, when they bring us these concerns, we are looking at people. We are not looking at statistics.

And so we have to depend upon whatever data that we can get to support the diagnosis or the prognosis of whatever we need to do to try to deal with the individuals, the people.

Dr. TOLLERUD. Of course, and that is what we tried to give you in the best way we can as scientists in the document that you have and the information we have. It is the best job that we collectively can do.

Mr. BISHOP. Anybody else? [No response.]

Well, since I have got a yellow light, let me just say that we have to deal with people, too, and just as you want to deal with a patient who comes and sits before you as an individual and you take the information that you have and try to address their concerns and their needs, so do we have that obligation, and we are trying to take the information that you have given us, and it looks like we have got a problem that ought to be dealt with.

But, of course, we cannot say with statistical certainty that there is a correlation because we cannot get that from you, but it looks like as you would try to deal with your patient, we need to deal with our constituents the same way.

Mr. HUTCHINSON. Thank you, Mr. Bishop.

Ms. Brown, you are recognized.

Ms. BROWN. Thank you, Mr. Chairman, and thank you for holding this hearing.

I would like my statement included in its entirety for the record.

[The prepared statement of Congresswoman Brown appears on p. 60.]

Mr. HUTCHINSON. Without objection.

Ms. BROWN. I would like to know how many women were exposed to Agent Orange. Were any women involved in this particular study? Have there been any other studies that included women? And lastly, do you think it would be beneficial to study mothers who have given birth who may have also been exposed to Agent Orange or other pesticides?

Dr. TOLLERUD. Excellent, excellent questions. I think the specifics of the number of women who served in Vietnam are better answered by the Panel 2 individuals from the Department of Veterans Affairs. I think they have very good data on that, and I will defer the latter part of the question to Dr. Olshan and to other committee members.

What I can say is that the Committee is extremely sympathetic to the concerns that you have raised and, in fact, in the document itself there is explicit language indicating that there is great interest in looking at women who were exposed, in particular, the women veterans who served in the war and their particular exposure and health outcomes in those individuals, many of which cannot be studied obviously in the male populations which were the largest groups that served in Vietnam.

So I think the Committee is very sympathetic and found with enthusiasm the movements that are already well underway by the VA and other groups to look at women's health effects, and perhaps Dr. Olshan can add.

Dr. OLSHAN. I just would agree that we support research of female veterans, and my understanding is that the VA has begun conducting studies of reproductive health of women veterans.

Dr. ERICKSON. I think I perhaps should respond to the part of your question about were there women involved in the studies that have been done, and the simple answer to that question for both CDC studies is, no, they were studies of male veterans.

Ms. BROWN. So there have not been any studies that involve females?

Dr. ERICKSON. Not done at CDC, ma'am.

Dr. MICHALEK. There are studies proposed and, I think, even begun, but you can hear that from the VA. I think they have a study planned on women Vietnam veterans. All of the Ranch Hand and control veterans in our study were men.

Ms. BROWN. I see.

Dr. TOLLERUD. I think a broader answer to your question is tied up in the nature of the means by which people have historically been exposed to herbicides and to dioxin. The Vietnam theater was one. Industrial accident is another, and those were, again, largely male worker populations.

There were women exposed in some situations, but the numbers were small. I think there are a number of studies cited in the report of larger population groups and of other occupational groups where women, in fact, were included.

There has always been an attempt to include women and include other smaller subgroups. It is just if they are not the dominant group, if they are a smaller group, it becomes very hard to study rare events. So I think there has been a scientific attempt to do that, but I think that what the VA is setting out to do is perhaps the best opportunity to continue that.

Ms. BROWN. Thank you.

Mr. HUTCHINSON. Thank you, Ms. Brown.

Mr. Tejeda.

Mr. TEJEDA. Thank you, Mr. Chairman.

I just have a quick question, one last question that perhaps you can answer, and I would certainly like Dr. Kizer to hear this question because I will be asking it of him also.

I know of several Vietnam veterans that have died at young ages and some because of cancer. Can you or the VA provide information on how many veterans have died, if any at all, because of Agent Orange?

Dr. TOLLERUD. Speaking on behalf of the Committee, we do not have that kind of specific information. We were able to estimate the number of veterans who would have died from various conditions assuming no exposure to Agent Orange, but the number who may have died because of exposures was not information that we had available.

Mr. TEJEDA. Thank you, Mr. Chairman.

Mr. HUTCHINSON. Thank you, Frank.

Are there other subcommittee members who have questions of this panel?

Before I excuse you, will there be ongoing reports issued, if not from the Committee, from other sources? The IOM will not have a legal obligation to issue a report for 2 more years. Do you antici-

pate that the Committee either will be taking some ongoing actions or do you anticipate other reports being issued subsequent to now, but prior to the 2-year mandate for the IOM?

Dr. TOLLERUD. I think we may get a response from the Institute of Medicine itself. From the standpoint of our committee and this report, our work is done at this point. I am aware of other related activities by the Institute of Medicine, including the exposure assessment committee on which I will also participate, which will have a report out. I do not know the timetable of that report, but there will certainly be intervening activities.

I would hope that the process toward the next report in 2 years would begin in the relatively near future, and that that could generate information, and certainly we expect that there will be scientific reports. It sounds like there are already several publications that will come out of Ranch Hands, perhaps something more from the CDC, perhaps something more from NIOSH, which also has a large interest in this.

So there will be new information coming out all the time.

Mr. HUTCHINSON. From your experience and involvement in this whole issue, are you optimistic that there is sufficient data available that we will be able to make a more conclusive, dogmatic conclusion than what the Committee reached in its report?

Dr. TOLLERUD. I am very optimistic. I do not know about the time frame. I do not know about 2 years from now, but I am very optimistic that there is an enormous amount of information that is available, that different researchers have, that different institutions have, that has not been plumbed to its fullest. There are new approaches. Computers are more powerful. So I think there is an enormous amount more that can be learned from existing data.

Whether that will be sufficient to answer the questions, I think, I am very confident that all of the questions will not be answered, but I think that some of these issues that have been raised today will, in fact, be clarified.

Mr. SMITH. Mr. Chairman, just one additional question, and in follow-up to the gentle lady from Florida. Dr. Kizer reminds us in his testimony that the study of reproductive health outcomes among women Vietnam veterans, Phase 1 was completed in March of 1995. Phase 2 is expected to be included in 2 years. It is a study of a total of 5,000 women that had been mandated as a result of the 99th Congress, Public Law 99–272, which goes back to the mid–1980s.

What kind of relationship, and, Dr. Tollerud, this would be to you, would your committee have with the data that was generated from this study? Does that get folded into your analysis? Is there any kind of relationship there?

Dr. TOLLERUD. I am not aware of any specific relationship. I think that is a very important scientific study which will be ongoing. As those data are generated and published, they will be made available to a committee of the Institute of Medicine, as well as the broader scientific community. So I think we will certainly have access.

And I might say that all of the groups, the governmental groups, the regulating groups, the scientists in the community, have all been extremely helpful and forthcoming to the Committee, coming

and giving testimony, presenting data that is not yet published, in fact, telling us what is on the horizon for the next ensuing years. So we have been very impressed with the openness of both the government agencies and the scientific community in providing us with information, and I am enthusiastic that that will continue.

Mr. SMITH. Just an opinion, and anyone who might want to venture a guess on this. Since this was mandated by the 99th Congress, are the results and, you know, the time that it has taken to get this off of the ground within the normal parameters of time that it usually takes to do this or is it slow, tardy?

It seems, you know, a layman's view would be why has this taken so long, that we are not even into Phase 2 yet.

Dr. TOLLERUD. I will maybe leave it to my epidemiology colleagues. I can say from a generic standpoint, it always takes much longer than you think when you are dealing with large population studies.

Dr. MICHALEK. Well, for example, it took us almost 6 years to retrieve medical records on 10,000 children. We were fortunate enough in the interim for the CDC chemists to invent the dioxin assay.

So as we carry on this process of Agent Orange research, there are technological breakthroughs that occur that allow us to do things. The assay is one example. We are working as fast as we can.

Mr. SMITH. My understanding, this is 5,000 women, and they have already gone through in Phase 1 500 women in selection. I am just trying to see whether or not this has been a priority within the VA to get to the bottom of this.

Dr. TOLLERUD. I think perhaps the next panel could address that.

Mr. SMITH. Well, I am just asking for your expert opinion.

Dr. TOLLERUD. Personally I have no information on the mechanism of that, what the difficulty is. I cannot comment.

Dr. MICHALEK. Verifying conceptions and birth defects, as you will learn, is a very arduous task. Each State has its own laws regarding access to medical records, and this is a very large detective effort to find people and get permission to get records and then locate the doctors and have those records copied and have them mailed and then have them reviewed and coded by medical records specialists and then reviewed by a physician. This is a very, as you see, complicated effort.

Mr. SMITH. But it would seem to be even more complicated for a child as opposed to a woman who is a veteran.

Dr. MICHALEK. Yes.

Mr. SMITH. Which would lead to the view that perhaps this should have been done sooner rather than later. It is half the number of people.

Dr. MICHALEK. Oh, well, I cannot comment on the VA effort. I am just talking about Ranch Hand.

Mr. SMITH. Thank you very much. I appreciate it.

Mr. HUTCHINSON. We thank all of our panel members. Thank you for being willing to come today and for your good answers and good presentations. You are excused.

Before you are excused, Mr. Tejeda has one more question. You are just not going to be able to get away.

Mr. TEJEDA. Thank you very much and thank you all. Just a brief question and something I read on the executive summary, and if I may, it is Table 1–1.

Dr. TOLLERUD. Yes.

Mr. TEJEDA. Updated Summary of Findings in Occupational, Environmental, and Veterans' Studies Regarding the Association Between Specific Health Problems and Exposure to Herbicides. It is on page 5 of the executive summary.

There are several things: sufficient evidence of an association, limited but suggestive evidence of an association, inadequate, insufficient evidence to determine whether an association exists, inadequate, and they go down, limited suggestive evidence of no association.

I was just wondering when you mentioned the word "limited" in there, when it is down there, does that mean that some people or veterans perhaps or their children perhaps did come out with that association with whatever it may have been, whether it was bladder cancer or if we are talking about inadequate? Well, inadequate, you are saying not at all, but on some of the limited, where it says limited, does that mean that there were some that may have had that or had that, but may have had it as a result of?

Dr. TOLLERUD. I think, speaking on behalf of the Committee, I think it is very difficult to apply those terms to individuals. They were really designed to look at studies and the weight of evidence of studies and specific investigations. So the term applies to the strength of evidence lumping a bunch of studies together, and I think it is very difficult to apply and beyond my means to be able to apply that to looking at specific individuals or veterans.

You have to recall that for most of the outcomes, in fact, for I believe all of the outcomes, except for birth defects, these categories were based on studies of populations other than veterans. They were based on either industrial accident populations, by and large, or people who were environmentally exposed.

So that is just an example. Certainly that does not imply that all individuals, including veterans who may have been exposed, will not have the same incidence of health effects as somebody else who did not happen to be a veteran, but the categories of evidence were based on epidemiology studies and not on specific populations of veterans.

Mr. TEJEDA. One last thing. If X number of veterans had passed away, let's say, by 1985 or by 1990, before you all started, you all do not have contact with that or do a study of that or were not presented with information as to that, as to what happened there?

Dr. TOLLERUD. You are saying for all veterans or all Vietnam veterans?

Mr. TEJEDA. That is correct.

Dr. TOLLERUD. Is that your question? That is correct.

Mr. TEJEDA. Thank you very much, Mr. Chairman.

Mr. HUTCHINSON. Thank you, and we appreciate the panel's indulgence today. Thank you very much.

I would now like to welcome our second panel this afternoon. This panel is composed of Dr. Kenneth Kizer, Under Secretary for

Health at the Department of Veterans Affairs. He is joined at the witness table by Dr. Susan Mather, Chief Public Health and Environmental Hazards Officer; Mr. J. Gary Hickman, Director, Compensation and Pension Service; and Mr. Walt Hall, Assistant General Counsel.

I want to thank the panel for their patience. Dr. Kizer, it seems like I say that a lot to you when you come to testify before our subcommittee. We are always delighted to have you, and you are recognized.

STATEMENT OF KENNETH W. KIZER, M.D., M.P.H., UNDER SECRETARY FOR HEALTH, DEPARTMENT OF VETERANS AFFAIRS ACCOMPANIED BY SUSAN MATHER, M.D., M.P.H., ASSISTANT CHIEF MEDICAL DIRECTOR FOR PUBLIC HEALTH AND ENVIRONMENTAL HAZARDS; J. GARY HICKMAN, DIRECTOR, COMPENSATION AND PENSION SERVICE; AND WALT HALL, ASSISTANT GENERAL COUNSEL

Dr. KIZER. And it is always a pleasure to be here, sir.

Mr. HUTCHINSON. Was that really sincere?

Dr. KIZER. Of course it was.

Well, good morning, and thank you, Mr. Chairman and members of the subcommittee. It is a pleasure to be here, and I welcome the opportunity to engage in this dialogue.

You have already introduced the other members at the table with me, so I will forego that. Your discussion with the previous panel has really covered the highlights of the most recent report by the Institute of Medicine on Agent Orange, so I am not going to review anything or say anything in that regard. I would like to confine my brief oral comments this morning to three things.

First, very briefly, I will discuss the process the Department of Veterans Affairs is following to review the IOM report and our planned time line.

Second, I would like to discuss some concerns that I have had about the potential for military service to be a risk factor for birth defects and what we would like to do about it at this point in time.

And third, I would like to update you on a relevant VA research project that has already been touched on this morning.

As you know, upon receipt of the recent IOM report, Secretary Brown established a special task force to review the new findings and to make recommendations to him. I chair this group. The other task force members include my counterpart at the Veterans' Benefits Administration, Mr. John Vogel, as well as Mary Lou Keener, the VA's General Counsel; Dr. Lynn Goldman, an Assistant Administrator of the Office of Prevention and Pesticides and Toxic Substances at the Environmental Protection Agency; Dr. Richard Jackson, the Director of the National Center for Environmental Health at the Centers for Disease Control and Prevention; and Dr. Frances Murphy, a neurologist and public health specialist who is Director of VA's Environmental Agents Service. We are supported by a working group of experts and policy makers from the VA, the Centers for Disease Control and Prevention, and the National Institutes of Health.

So far, the task force has had two meetings. We have another meeting scheduled for April 23, at which time we will be taking

comments from veterans' service organizations, as well as other groups interested in this subject. We will be soliciting their input on the science, as well as making sure that we have all of the scientific data that we need to have before we make the recommendations that we expect to make to the Secretary.

We expect to complete our review and have those written recommendations to the Secretary by the second week of May.

Shifting to the second subject, I think this most recent report by the IOM underscores an issue that I have discussed internally in the VA on several occasions in the past 18 months that I have been associated with the agency, and the report has prompted me to speed up a previously envisioned time line.

And to give a little background and put this in context, as a medical specialist in toxicology and occupational health, and one who has been a public health official for most of the past decade, I have had to repeatedly deal with questions and concerns about untoward or adverse reproductive effects in a variety of populations who are, or have been, exposed to industrial, agricultural or other work environments that are very similar to those of our active duty military personnel.

However, in coming to the VA and specifically looking at what is available in this regard—that is, as far as looking at reproductive outcomes and what these environmental effects may be among our veterans, we find that there is little to support conclusions in this regard. I find that both surprising and of concern.

This concern is heightened by the recent change in the demographics of the active duty population. Now, up to 20 percent of active duty personnel are female. This is particularly of concern since maternal exposure to toxicants is more commonly associated with adverse pregnancy outcomes than paternal exposures, although I would hasten to add that we know from male agricultural workers, among others, that untoward reproductive effects certainly can occur among males.

In any case, the bottom line is that I believe that not enough attention has been directed towards potential environmental reproductive hazards of military service. To address this deficiency, we are planning to establish a VA Environmental Hazards Research Center for Reproductive Outcomes.

As you know, we have a number of environmental hazards research centers already in place, particularly looking at issues related to the Persian Gulf War. One of the issues that has repeatedly come up with regard to Persian Gulf veterans is also the issue of adverse reproductive outcomes. Here is another situation where I think we need to have an infrastructure that allows us to pursue these questions both retrospectively and prospectively.

We would propose that this center be specifically dedicated to investigating reproductive outcomes among veterans and their offspring. Since VA data banks are limited with respect to information on reproductive outcomes and veterans' offspring, we see this as needing to be a collaborative effort, one in which VA works with other federal or state agencies that already collect birth outcome data. VA would work with agencies that collect information on relevant chemical exposures, whether they be in the industrial, agricultural, military or other environments. In doing this, VA will

need to obtain information that is drawn from an ethnically and culturally diverse population that reflects the composition of the active duty military population.

We will be keep the Committee apprised of our progress as we proceed in this regard.

Finally, let me just very briefly mention, a research project that the VA is conducting. This is the retrospective cohort study comparing the reproductive health outcomes of 5,000 women Vietnam veterans to those of an equal number of women veterans who did not serve in Vietnam.

This study will certainly add to the knowledge we have with respect to birth defects among offspring of women Vietnam veterans.

The feasibility portion of this study, or Phase 1, was largely completed in March 1995. It showed that the study can be accomplished. There was a very high response rate of over 85 percent of the living veterans; that is an exceedingly good response for this type of study.

The full study will be pursued, and we expect to have those results in 2 years. I know questions were asked earlier about why it has taken this long. As I understand it, there have been a number of methodological issues and concerns that have had to be addressed in setting up the study. Those have been resolved and the study is now moving forward very rapidly with a very good response.

In conclusion, let me underscore the need for more research regarding the possible reproductive effects of military service. This is an area that has not received adequate attention in the past and one that should be a high priority for us in the future.

I thank you, again, for the opportunity to be here this morning, and I would be happy to respond to your questions or comments.

[The prepared statement of Dr. Kizer appears on p. 123.]

Mr. HUTCHINSON. Thank you, Dr. Kizer.

You mentioned in your opening statement regarding the timetable for the recently formed VA task force, and I think you said the second week of May you expect recommendations to be issued. Without asking you to tell us what the recommendations are, in what area will the task force be making recommendations?

Dr. KIZER. Briefly, the recommendations would be to recommend to the Secretary whether the data as presented by the Institute of Medicine, along with whatever other data is available, is sufficient that it should be considered for action by the Secretary for potential compensation or other benefits.

Mr. HUTCHINSON. My understanding is though that under the law currently, it would require congressional action when we're talking about the children of veterans who are affected, that there is not current legal authorization. Am I correct on that?

Dr. KIZER. Well, you are correct with regard to that subset. The overall charge to the Committee is to look at all of the data and all of the conditions and make recommendations to the Secretary. With regard to the specific issue of dependent children, you are correct. Our general counsel would concur that the Secretary does not currently have the authority to take action. That authority would require congressional action.

Mr. HUTCHINSON. So would the task force, if they felt the data justified it, recommend then to the Secretary that he seek congressional changes? Would that be within the purview of what the task force would be doing?

Dr. KIZER. The scenario that you hypothesize would be within the purview of the Committee.

Mr. HUTCHINSON. Dr. Kizer, you mentioned in your statement something about your own involvement and expertise in the field of neural tube defects. Could you expand upon that a little bit concerning your experience with veterans with spina bifida in the State of California?

Dr. KIZER. I cannot specifically relate it directly to veterans per se, other than insofar as there are a large number of veterans in California. A number of the programs we put in place in California are very germane to this.

During my tenure as Director of Health for California, we put in place a statewide birth defects monitoring program that would provide information on birth outcomes of all of the residents of the State, including veterans.

We also put in place the largest neural tube defects screening program in the world at that time, and so that information was available for the entire population of women choosing to be tested.

During my tenure in California we also had a number of environmental incidents related to dioxins. For example, in 1987, there was what has become known as the Kopper's fire. It was a fire at a wood reprocessing plant in Northern California in which pentachlorophenol was burned. One of the contaminants in the fallout was dioxin, and that covered a large area. A number of studies are ongoing trying to assess what the effects of that might be on the population that was affected by that fallout.

We were involved in a number of studies looking at dioxin contamination in fish and water fowl in rivers consequent to the effluent from paper processing and wood processing mills. There were a number of other situations in which dioxin contamination was an issue, including situations involving herbicides.

Mr. HUTCHINSON. From your own expertise and experience, do you have an opinion regarding the IOM update on the limited suggestive evidence of an association on the two new areas, including the spina bifida?

Dr. KIZER. Well, insofar as I am here as a representative of the Department of Veterans Affairs, I will confine my comments this morning in that vein.

Mr. HUTCHINSON. How many members are there on the task force?

Dr. KIZER. There are seven.

Mr. HUTCHINSON. Seven?

Dr. KIZER. That's correct.

Mr. HUTCHINSON. Those were appointed by the Secretary; is that correct?

Dr. KIZER. Yes.

Mr. HUTCHINSON. You may have covered this, but remind me of their background. What area? Are they all from within the VA?

Dr. KIZER. No, as I mentioned, Dr. Dick Jackson, who is the Director of the National Center for Environmental Health, is a pedia-

trician by training with considerable expertise in toxicology and is a renowned expert in this regard.

Dr. Lynn Goldman, from the Environmental Protection Agency, is also a pediatrician by training and is well known for her work in toxicology in general, as well as specifically in the area of dioxins.

Dr. Frances Murphy, who heads our Environmental Agents Service, is a neurologist by training, with special expertise in public health.

So the Committee has a broad based background, and while the VA per se may not have institutional memory, if you will, in the area or experience in the area of birth defects, I think this committee is well represented in that area, both technically and from a policy point of view.

Mr. HUTCHINSON. Thank you.

You have me very curious about your personal opinion now in this.

Mr. Edwards.

Mr. EDWARDS. Mr. Chairman, I would like to yield my time to Mr. Evans.

Mr. HUTCHINSON. Mr. Evans, you are recognized.

Mr. EVANS. Thank you, Mr. Chairman. I thank the gentleman for yielding.

Doctor, could you submit to us actual legal opinion from the General Counsel concerning the eligibility of children for benefits or services?

Dr. KIZER. Yes. We will be pleased to provide that opinion for the record.

Mr. EVANS. Has the task force consulted with the Administration of the Agent Orange Class Action Program, which has been funding programs to serve Vietnam veterans' children with disabilities for the past 7 years?

Dr. KIZER. I am sorry. I did not hear the first part of that.

Mr. EVANS. Has the task force consulted with the Administration of the Agent Orange Class Assistance Program, which has been funding programs to serve Vietnam veterans' children as a result of the lawsuit years ago, children with disabilities for the past 7 years?

Dr. KIZER. They have been invited to provide comments on the 23rd, along with a number of other groups that are particularly interested and concerned about this issue.

Mr. EVANS. Including the Spina Bifida Association of America?

Dr. KIZER. As I recall, they have been invited to it as well.

Mr. EVANS. Does the VA at present have any expertise either nationally or at any one of its medical centers in dealing with pediatric disabilities, such as spina bifida?

Dr. KIZER. VA has not included pediatrics historically, and I am not aware of any particular expertise that resides within the system in this regard.

Mr. EVANS. Well, if this Congress decides to provide medical care to children with spina bifida whose mothers or fathers served in Vietnam, would the VA medical system in your opinion or professional opinion, whatever you would like to offer, be the appropriate primary delivery mechanism for that care?

Dr. KIZER. I would have to look at it and see exactly what was involved, but as a first pass or at least as a first guesstimate, I think we would be looking at some sort of contractual or sharing arrangement to provide that care.

There is other relevant expertise such as neurosurgical, but I suspect if I were a parent with a child in this regard, I would probably want to go to the folks who handle the cases most often, and that would not be the VA in this case.

Mr. EVANS. Right. Dr. Mather, have you been able to extract any useful information about spina bifida from the Agent Orange registry as to the numbers of cases in the registry or the needs of children and their families?

Dr. MATHER. The registry only asks questions about birth defects and did not go into specific birth defects.

Mr. EVANS. All right. I thank the gentleman for yielding, and I thank the Chairman for the time.

Mr. HUTCHINSON. Mr. Tejeda.

Mr. TEJEDA. Thank you, Mr. Chairman.

Dr. Kizer, you heard one of the questions that I asked, and I will reask it to you. I have heard from many veterans, and there is hurt and some frustration. I have heard from many, as I mentioned, Vietnam veterans.

You know, it has been about 25 years since we stopped using that Agent Orange, and are we still calling for more research or is research going on right now to see what can or cannot be done by the VA?

Dr. KIZER. If I understand your question correctly, I would have to answer yes on two and no to a third of three different parts of what you were asking.

Is there a need for more research? Absolutely.

Is there research underway and ongoing? Yes, there is.

Finally, you did not ask, but I think it is implied in what you were asking, is the research going to be able to answer the questions that you have and our veterans have? And the answer to that I would say is no. There are many things that, frankly, science is just not going to be able to answer, and certainly not going to be able to answer in a timely manner. It is going to come down to making public policy decisions based on the best information that we have, which I think, as the last panel would agree, is scientifically inadequate to come to the sorts of conclusions that you would like to have.

Mr. TEJEDA. Why in your opinion can't some of these questions be answered?

Dr. KIZER. In many cases, the science is just not there. The ability is not there to answer the question. The most glaring deficiency in not only in this area, but in lots of areas regarding toxicological exposures. It is one which you alluded to quite graphically in one of your prior questions and has to do with the question of exposure. If, for example, you happen to have been a Navy Seal in Vietnam crawling around in the mud and being in the jungle without taking a bath for days or weeks on end, what was that exposure versus the exposure of someone else who did not have that type of experience?

There is just no way the science can answer those questions about exposure, and in toxicology the whole issue is dose, or exposure. If we do not have the basic information on exposure, then no matter how good the scientific studies are, they are not going to be able to answer questions about the causal connection which really is the basic question.

Mr. TEJEDA. Well, research certainly is very important, but there are many veterans who need concrete answers and help as to their health care concerns. Let me now ask you that question that I asked earlier.

Can you or the VA provide information on how many veterans have died because of Agent Orange?

Dr. KIZER. In answering your question, I have to qualify it based on the discussion that we just had. Insofar as science cannot answer whether exposure to dioxin may have caused it; that question is unanswerable.

Can the VA provide you with information on the numbers of veterans who have died with a variety of conditions, some of which have been statistically associated with Agent Orange? The answer to that is yes, but even in that case, as was commented upon earlier, that statistical association does not necessarily mean cause and effect.

Mr. TEJEDA. Is the VA at this point taking care of some veterans who have been exposed to Agent Orange?

Dr. KIZER. Absolutely.

Mr. TEJEDA. On the broader issue of Agent Orange exposure, what does the VA intend to do with the new IOM data?

Mr. TEJEDA. Well, as was discussed previously with the Chairman, it is premature to answer that. We still have another meeting. We have invited folks to provide additional data. It certainly would not be fair to those other groups who have been asked to present information to us to say what we are going to do now without the benefit of their input.

Mr. TEJEDA. Thank you, Mr. Chairman.

Mr. HUTCHINSON. Thank you, Frank. Mr. Smith.

Mr. SMITH. Thank you very much, Mr. Chairman, and, Dr. Kizer, thank you for your testimony, and I would appreciate it if you would get back to us as you indicated in your testimony with regards to the study on women, the study that was mandated by the 99th Congress.

I think it would be good for us to be updated and to know why. Again, that predates your tenure, so I can understand why you might not know why all of that seemingly has taken so long, and maybe there are some good, valid explanations and we just need to know about it.

I would like to ask you. You spoke of the VA Environmental Research Center for Reproductive Outcomes, and I was wondering if you might tell us. You said it would be funded internally with, I guess, no new need for appropriations for that. How much do you anticipate it will cost?

You indicated by July 1 you hoped to have, I guess, the proposal out and awarded. Exactly what would the center do? Where would it be located? What is the proposed staffing? What kind of services,

if any, would be provided? Is it purely investigatory or is it a service provider?

Do you intend to collaborate with the DOD on this or is that something that has not been factored into it? And anything else that you can tell us about it that would be relevant.

Dr. KIZER. Specifically the answers to most of the questions you asked would be premature to answer yet. The reason simply is that we want to get the best possible location for this activity, and the way to do that is to issue a request for proposal. Until we have issued the request and gotten the responses back, we cannot answer the things about where and who is going to be involved and what our collaborative arrangements may be.

We would expect as a requirement, given the limitations of VA's experience in this regard, that it will require a collaborative effort between multiple agencies, probably at both the state and federal level. That will probably, by default, limit the number of potential respondents to the request for proposals.

And let me just digress briefly. This is something we have talked about in the VA going back to shortly after I came on board. We have initiated a complete review of VA's research program. The initial plan was to wait until the Research Realignment Committee had given its report and we had had a chance to look at that before we specifically proceeded with regard to the research center. Now, we have agreed internally, at least, that this is something that needs to be done now. It probably should be considered however within the context of the larger assessment of the VA's total research program.

With the issuance of this latest NAS report, we feel that we need to speed the time line up. We are going to go ahead and proceed with citing this before the Research Realignment Committee has issued its report. We do not see that as a major problem.

Establishing a research center will take some time given the process to issue an RFP. It takes time to get responses back and to evaluate those responses with an appropriately convened scientific group. It is going to take 3 months or so, if not longer. So actually the amount of funding that would be required in the current fiscal year is probably on the order of $50,000, because it will be basically to initiate the center only.

We would anticipate being able to fund at least the start-up and the initial efforts of the center out of our research funding in fiscal year 1997. As the program evolves, and as it started to unfold its research agenda, then we will be in a better position to talk about ongoing funding needs. Perhaps those ongoing needs are something that could be met by multiple entities.

Those are all logistical details that need to be worked through, and that will be worked through, and but they do not preclude moving forward with the center it at this point.

Mr. SMITH. I know it is all preliminary, but do you have any sense as to how many staffers would be tasked?

Dr. KIZER. How many staffers would be tasked?

Mr. SMITH. Actually working at the center.

Dr. KIZER. I think I could only give you a ball park figure.

Mr. SMITH. That is okay.

Dr. KIZER. I think somewhere in the range of six to ten would be a good point to start with, recognizing that it may well need to be expanded. As with many investigatory efforts, it would probably involve the part-time efforts of a number of investigators and clinicians who may be spending 20 percent of their time doing research and 80 percent of their time seeing patients or something of that type.

So at this point, it is impossible to give you a specific figure. We want to start it up, get it going, and then let it mature according to what the needs are.

Mr. SMITH. What kind of services do you anticipate being provided by the center?

Dr. KIZER. Well, initially we see it as a research center that would specifically focus on the environmental hazards of the military environment and what potential effects on reproductive outcomes might result form these hazards.

Mr. SMITH. But you will be seeing patients. I mean, what would the doctors actually be doing? Just gather information or providing recommendations for actions? What would they be doing?

Dr. KIZER. As a research center, I would see it being involved in epidemiologic investigatory efforts, possibly laboratory or "wet lab" science, as it is sometimes called, and probably other clinical projects in which patients would be involved as subjects.

At this point we have not laid out a specific research agenda. That is part of what we would like to see in the response to the RFP.

Mr. SMITH. If I could continue just a moment longer, Mr. Chairman?

Mr. HUTCHINSON. Without objection.

Mr. SMITH. Thank you.

You mentioned $50,000 for 1996. What would be the estimation, again, ball park for 1997?

Dr. KIZER. Recognizing that you are not going to hold me to this number because we are merely talking ball parks here, our other environmental research centers are funded at a rate of about $500,000 a year. We would see starting this Center at $300,000 to $500,000 and then would, as I said before, assess funding needs as the center matured.

Mr. SMITH. Finally, could you speak of the Agent Orange registry that was established in the 1980s and what is the status and has that information been tracked?

Dr. KIZER. I will just note that as I recall, there are about 250,000 people on that registry. It has been used in a variety of studies, and I am going to defer further comments to Dr. Mather.

Dr. MATHER. I think basically it was a way of allowing veterans to register their concerns, and we have as Dr. Kizer said seen about 250,000 at this point. The amount of information that we have computerized from that registry is somewhat limited, and I think we have learned a lot from that registry which we applied to the Persian Gulf War registry, but certainly the actual information in the computerized data bank is much less for the Agent Orange veterans, and it was viewed primarily as a way we could begin to assemble a roster of veterans who served in Vietnam because, as you know, there was no list kept of everybody, no tapes.

The automated data processing was such 25, 30 years ago that we simply do not have a list of everyone who served in Vietnam. So it was a way of beginning to assemble that list and to get some basic data.

But it is not very extensive as far as, for instance, it did ask about birth defects, but we do not have data on what birth defects are involved.

Mr. SMITH. Dr. Erickson talked about the tremendous prevention opportunity with the folic acid. Is that something the VA should be broadcasting to female veterans?

Dr. KIZER. Well, the broad based approach of getting to all women with that information is something that, as a matter of public policy, we should be aggressively pursuing in all facets of government. Whether there are specific opportunities for us to increase, that is something we need to look at and pursue accordingly.

Mr. HUTCHINSON. Thank you, Mr. Smith.

Mr. Tejeda.

Mr. TEJEDA. Just one last question. I asked the question was the Veterans' Administration helping and serving Vietnam veterans who were exposed to Agent Orange. The answer was yes.

Do you have an approximate number of how many are being served because of Agent Orange?

Dr. KIZER. I do not have those exact numbers at my fingertip. We will certainly be happy to provide you with the information as far as what has occurred since those conditions were added on in 1993.

I would also, just as a further qualifier, note that insofar as Agent Orange is possibly associated with a number of untoward health effects, there are many veterans that we may be taking care of that are not identified as those having health effects specifically due to Agent Orange exposure, but they are still getting care and services from the VA.

Mr. TEJEDA. And it may have been because of Agent Orange or something?

Dr. KIZER. It may have been because of Agent Orange. It may have been for other reasons that we will never know.

Mr. TEJEDA. Thank you very much.

Thank you, Mr. Chairman.

Mr. HUTCHINSON. Thank you.

Are there other questions from the subcommittee? [No response.]

Dr. Kizer, let me just say in concluding the hearing this morning that we appreciate your testimony, and insofar as the subcommittee's role, I can assure you that we will be anxiously awaiting the recommendations of the VA's task force and their suggestions.

I think at that point we will need to make some decisions as to whether additional hearings are justified on this issue, as Mr. Evans has suggested; whether the additional research that is taking place is sufficient; or whether there needs to be some legislative role in mandating further research, and a determination as to whether or not any legislative changes need to be considered regarding benefits.

I look forward to working with you and Secretary Brown, Mr. Edwards, and Chairman Stump and Ranking Member Montgomery as we look at some of those decisions in the future.

Thank you again for your testimony today.
Dr. KIZER. Thank you, sincerely, for the opportunity to be here.
Mr. HUTCHINSON. The committee stand adjourned.
[Whereupon, at 12:50 p.m., the subcommittee was adjourned.]

APPENDIX

Opening Statement
of
Chairman Tim Hutchinson
April 16, 1996
Institute of Medicine Update on
Veterans and Agent Orange

The Subcommittee will come to order.

Today, the Subcommittee on Hospitals and Health Care meets in its oversight role to hear testimony on the recently released update by the Institute of Medicine (IOM) on an association between Herbicides and Diseases in Veterans who served in Southeast Asia. The update is in response to the congressionally mandated requirement of the Agent Orange Act of 1991 which requires the National Academy of Sciences to conduct an independent, comprehensive review and critical evaluation of the scientific studies and medical evidence concerning the health effects of herbicide exposure. Reviews are required every two years by the Act.

The study, released by the Institute of Medicine as a re-evaluation of the Agent Orange health questions, identified two new health effects in the category of a "limited or suggestive" association between herbicide or dioxin exposure. They are the acute transient form

of peripheral neuropathy (a neurological disorder that can lead to pain, numbness, and weakness in the limbs) in Vietnam veterans, and spina bifida (a congenital abnormality) in their children.

I would like to begin by stating that the Veterans' Affairs Committee has historically demonstrated a longstanding record of bipartisan support for those veterans who so nobly served this Country during possibly the most politically turbulent period in our history. Five members of the Full Committee are veterans of this era and I would like to recognize the service of Mssrs. Stearns, Bachus, Evans,Clement, and Tejeda. Over the years, individual members of the Committee such as Lane Evans have committed themselves to the resolution of issues affecting what is now the largest cohort of living veterans, the 8.5 million veterans of Vietnam and the Vietnam Era.

This morning we are fortunate to have on our first panel a group of eminent researchers, two of which -- Drs. David Erickson and Joel Michalek are authors of two seminal studies on Agent Orange. These are the 1984 **Vietnam Veterans' Risk for Fathering Babies with Birth Defects,** and the ongoing **Ranch Hand Study**. I also welcome Dr. David Tollerud, Chairman of the Institute of Medicine Committee to

Review the Health Effects in Vietnam Veterans and Dr. Andrew Olshan, a member of the committee who is a nationally recognized expert on reproductive health effects. I would like to personally thank each of the members of the Committee who served on the Institute of Medicine Committee to Review the Health Effects of Vietnam Veterans. Service on this committee was completely voluntary and without compensation.

The questions of cause and effect relationships between exposure to herbicides such as dioxin and service in Vietnam have from the very beginning been mired in controversy. The questions asked of the experts have been simple but finding the real answers have been long in coming. The experts before this Subcommittee today have spent countless years looking at the complexity of the problems posed by exposures to various chemical agents and their possible effects on the environment and its inhabitants, both plant and animal. This hearing is not an attempt to reach a final verdict on the issues raised by the IOM update but it is in an important step in ascertaining the possible needs for future Congressional action.

It should be understood that the Agent Orange Act of 1991 requires the Secretary of Veterans Affairs within 60 days of release of the Institute of Medicine report to determine whether additional presumptions of service connection are warranted for any of the diseases covered in the report. The recommendations of the VA Task Force and any subsequent action of the Secretary relates only to service connection of diseases suffered by veterans themselves; nothing in the Act governs policy decisions regarding health effects in the offspring of veterans. Such a change would require Congressional action. The purpose of this hearing is to help us determine whether such action is warranted.

Opening Statement
for
Honorable Chet Edwards
Ranking Member
Subcommittee on Hospitals and Health Care

Hearing on the Study by the Institute of Medicine
Veterans and Agent Orange: Update 1996

April 16, 1996
Room 334, CHOB

Mr. Chairman, I'd like to commend you for responding so quickly to the recent publication of the Institute of Medicine report on Agent Orange and scheduling this hearing. You have assembled an impressive lineup of witnesses. I hope the testimony we receive today will not only help us understand the report's findings and implications, but assist us in determining what actions should be taken next.

Among its most striking findings, the Institute of Medicine reported that there is new "limited or suggestive" evidence to

show an association between exposure to herbicides and the congenital birth defect spina bifida.

This finding has undoubtedly bolstered the hopes and expectations of numbers of veterans and their families. Yet the IOM report concedes that the evidence for such an association is inconclusive, and that "the pattern warrants further evaluation."

I welcome the opportunity to learn whether there is any promise or hope for further, more conclusive research or analysis, and what the prospects are for conducting such research or analysis in the near term.

Mr. Chairman, this hearing is itself only a first step. The Secretary of Veterans Affairs has assembled a task force to

conduct an in-depth review of the IOM report, and I look forward to the VA's findings and actions.

Finally, in reviewing the IOM report, we must also be mindful that VA's special authority to provide care to Vietnam veterans expires at the end of this calendar year. Whatever conclusions we reach on the subject of spina bifida, the IOM report certainly reaffirms earlier findings about the association between Agent Orange and many other diseases, and we must be sure to grant VA the authority it needs to continue to meet its treatment obligations to Vietnam veterans.

Rep. Joseph P. Kennedy II
Subcommittee on Hospitals and Health Care
April 16, 1996

Mr. Chairman, I would like to thank you for calling this meeting. I also would like to commend the Institute of Medicine for the extensive research they have completed - and the findings being reported to us today. It took the federal government more than 20 years to confirm that certain serious health problems of Vietnam veterans are caused by exposure to Agent Orange. Finally concrete research is being conducted - and concrete results are being reported.

Beginning in 1962, about 19 million gallons of herbicides were sprayed over South Vietnam to defoliate vegetation. Tens of thousands of the three million Americans who served in Southeast Asia are though to have been exposed to the chemicals. Yet the first report of the effects of the herbicide on the health of Vietnam veterans was not issued until 1993.

I would like to applaud VA Secretary Brown for the prompt action he took after the release of this first report. He moved quickly to provide presumptive compensation to Vietnam vets with certain conditions linked to exposure to herbicides. I have fought hard since them to ensure that the Vietnam veterans exposed to these herbicides continue to receive their just compensation.

In the report just released this March, the Institute of Medicine on the recently released follow-up to this 1993 report. In this 1996 follow-up, the Institute of Medicine confirmed previous findings. It also found a limited or suggestive link between Agent Orange and an above-average rate of spina bifida among children born to Vietnam Vets. In fact, babies born to Vietnam vets are up to 2 1/2 times more likely to have spina bifida than children born to non-veterans.

An association also was found between Agent Orange and a nerve disorder that can cause temporary numbness or pain.

Just as VA Secretary Brown took quick action in 1993, he responded likewise in 1996. On March 14, 1996 - immediately following the release of this report - Brown announced that he would form a task force to review the evidence NAS used to arrive at its conclusion.

Brown also announced that the VA will pursue research on birth defects among children of Vietnam veterans and reproductive health effects of Vietnam service. While there may not be enough evidence to concretely link exposure to Agent Orange to birth defects other than spina bifida, there is definitely enough evidence to warrant further research.

The results of the two Institute of Medicine studies give us hope that researchers are getting closer to answering the lingering questions about the health effects of herbicide exposures. For the first time, we have been provided confirmation of what we have long expected - there is now evidence of a distinct relationship between exposure to herbicides and a specific birth defect - spina bifida.

At the same time, science is still evolving. We have proven some associations in the present, and we don't know yet what we will prove in the future. Until more conclusive evidence is available, we should award compensation to veterans with illnesses that may be linked to Agent Orange exposure. It is crucial that we not cut off aid to veterans who deserve and need care.

Statement of Rep. Luis V. Gutierrez
Subcommittee on Hospitals and Health Care
April 16, 1996

Good morning.

Mr. Chairman, I would like to thank you for holding this important hearing to discuss the results of the recent study by the Institute of Medicine on the health effects in children of individuals exposed to Agent Orange.

I would also like to welcome our witnesses to these chambers.

Many of us here have worked on the Agent Orange issue before. This committee has authorized the National Academy of Sciences to make biannual reports such as the one we are discussing today.

In addition, this committee has authorized and re-authorized the Secretary of Veterans Affairs to provide presumptive compensation to Vietnam veterans diagnosed with such ailments as Hodgkin's disease and soft-tissue sarcoma among others.

I would like to commend the members of this committee, the National Academy of Sciences and Secretary Brown for the progress, in both understanding and care, that has been made with regards to Agent Orange exposure.

However, as the 1996 study demonstrates, there is more work to be done.

I would like to ask my colleagues to join me in urging Secretary Brown to give full and fair consideration to the results of the 1996 update with an eye toward the most comprehensive compensation that we can give to every man, woman and child affected.

There is a precedent for compensation for the illnesses that fall within the so-called "second tier."

The 1996 update found limited or suggestive evidence for the acute, transient form of peripheral neuropathy. Although this illness is of a temporary nature, and that poses some questions, I believe that the VA should provide a compensation mechanism to those who suffer from this ailment.

In addition, I would ask the members of this committee to work with Secretary Brown and other federal agencies to provide financial support to meet the special health care needs of children with spina bifida and their families.

We must ensure that the children of Vietnam veterans with spina bifida receive compensation and appropriate care. This will not be easily accomplished. Providing medical care and benefits to the dependents of veterans raises numerous questions?

I am aware that other institutions might offer better health care to children and young adults with spina bifida. I understand that VA expertise is focused in areas of greater concern to older veterans of the World War Two and Vietnam generations, as it should be.

However, I urge the Secretary not to base his decision on what can be done, but instead, on what should be done for these young people. I am hopeful that the VA Task Force will study possible inter-agency cooperation, with the Department of Health and Human Services' Administration for Developmental Disorders or other agencies that could team up to provide experience in caring for children with neural tube illnesses.

Mr. Chairman, I understand that the VA Task Force is mandated by the Agent Orange Act of 1991 to make recommendations to Secretary Brown by May 13, 1996.

I believe that it would be in the committee's interest to follow up this hearing with a policy-oriented hearing after those recommendations are provided to Secretary Brown. Receiving the testimony from the VSO's and family service groups would be very helpful in resolving the deep policy questions that lay ahead.

So Mr. Chairman, I strongly urge you to call for hearings on this issue prior to the Memorial Day recess.

At this point, I would like to make the committee aware of the irony surrounding the Agent Orange issue this year.

While new information was being uncovered by the Institute of Medicine with regards to spina bifida and peripheral neuropathy, veterans family service organizations, and the thousands of children that depend on their care, may lose their funding.

The Agent Orange Class Assistance Program will be out of money as of June, 1996.

This is an issue that cannot be overlooked by this committee or by the VA in searching for care mechanisms for veterans and their children.

Mr. Chairman, I look to forward to working with you on this matter in the future. Once again, I thank you for calling this timely hearing.

STATEMENT OF THE HONORABLE CLIFF STEARNS
HEARING ON EFFECT OF AGENT ORANGE
SUBCOMMITTEE ON HOSPITAL AND HEALTH CARE
COMMITTEE ON VETERANS' AFFAIRS
APRIL 16, 1996

THANK YOU, MR. CHAIRMAN. TODAY WE WILL HEAR TESTIMONY ON FINDINGS JUST RELEASED WHICH GIVES AN UPDATE ON THE EFFECTS OF VETERANS AND AGENT ORANGE. THE PRIMARY FOCUS IN THESE UPDATED STUDIES IS WHETHER OR NOT THERE IS A CONNECTION BETWEEN BIRTH DEFECTS OF CHILDREN OF THOSE SERVICEMEN WHO WERE SPRAYED WITH HERBICIDES WHILE SERVING IN VIETNAM.

PREVIOUS STUDIES CONDUCTED BY THE NATIONAL ACADEMY OF SCIENCES FOR THE DEPARTMENT OF VETERANS AFFAIRS AT THE DIRECTION OF CONGRESS FOUND A LINK BETWEEN AGENT ORANGE AND THAT AT CERTAIN LEVELS IT CAUSED A PLETHORA OF CANCERS AND OTHER HEALTH HAZARDS. FROM THE DATA ON THE RESEARCH CONDUCTED AS RESULT OF THIS INITIATIVE, THE STUDY CONCLUDED THAT THERE WAS SUFFICIENT EVIDENCE OF ASSOCIATION BETWEEN HERBICIDE EXPOSURE AND SOFT-TISSUE SARCOMA, NON-HODGKIN'S LYMPHOMA, HODGKIN'S DISEASE, CHLORACNE AND PORPHYRIA CUTANEA TARDA.

IN READING THE VARIOUS TESTIMONIES FOR TODAY'S HEARING, I BELIEVE THAT SUFFICIENT EVIDENCE HAS BEEN PRODUCED TO ENCOURAGE FURTHER STUDIES OF THE POSSIBLE LINK BETWEEN BIRTH DEFECTS, SUCH AS SPINA BIFIDA, AND CHIDLREN BORN TO VETERANS SPRAYED WITH HERBICIDES DURING THE VIETNAM CRISIS.

I WELCOME THE TESTIMONY OF THE VARIOUS ORGANIZATIONS CONNECTED WITH THIS STUDY AND THE SERVICE ORGANIZATIONS ASSEMBLED HERE. IT IS MY HOPE THAT FURTHER STUDIES MAY BE CONDUCTED SO THAT WE HAVE A FINAL PRONOUNCEMENT AS TO WHETHER OR NOT AGENT ORANGE IS CULPABLE FOR CAUSING SUCH DEFORMITIES IN CHILDREN BORN TO VIETNAM VETERANS.

THANK YOU, MR. CHAIRMAN.

HEARING:

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
HOUSE COMMITTEE ON VETERANS AFFAIRS

OPENING STATEMENT BY
CONGRESSWOMAN CORRINE BROWN

Mr. Chairman, thank you for holding this important hearing today. The lasting effects of Agent Orange exposure by our Vietnam Veterans is a true tragedy. And to now be discovering new connections between this chemical and adverse health consequences is truly heartbreaking.

However, as we owe the largest debt of gratitude to our veterans who suffer the health effects of fighting our nation's wars, we owe our veterans the answers to the questions they ask. Vietnam veterans that I talk to want the exposure

to Agent Orange fully examined and explained. Thankfully, we are now studying the effects to give a little bit of relief to our veterans exposed to these chemicals.

Earlier this year, the House passed a bipartisan bill which extended for two years VA's authority to provide health care for veterans exposed to Agent Orange. The bill also permanently extended similar authority for veterans exposed to ionizing radiation. Passing that bill proves how well this committee has worked together to address important problems. And I thank Chairman Hutchinson for holding this

important hearing today.

Just as our Vietnam Veterans made valiant efforts for our nation, we owe them our most valiant efforts to explain and identify the effects of this horrible chemical. I look forward to hearing the testimony we are about to receive on this very important issue.

Statement of Rep. Michael P. Flanagan of Illinois
VA Hospitals and Healthcare Subcommittee Hearing
Effects of Agent Orange
April 16, 1996
10:00 AM 334 CHOB

Opening Remarks

Thank you Dr. Tollerud, Dr. Kizer and all of you for coming here today to testify before this Subcommittee regarding the effects of Agent Orange. I would like to join my colleagues on this Committee in welcoming all of you to Washington, DC today. We all certainly appreciate your dedication and commitment and are happy to have you here.

Exposure to the herbicide Agent Orange has been associated with the development of different cancers, nerve disorders, birth defects, high infertility rates and miscarriages. I think that all of us will agree that those veterans exposed to chemicals such as Agent Orange and other environmental hazards deserve priority healthcare.

Quality and accessibility of veterans' health care is a priority of Chairman Stump and the this Committee as a whole. We must move forward to ensure that our veterans receive the very best in health care, in an efficient

manner.

I look forward to hearing and reviewing the testimony of Drs. Tollerud and Kizer and working on this Subcommittee to address the effects of Agent Orange and make the appropriate decisions so that those affected will receive the best care possible. This is the least we can do to reaffirm our commitment to our Veterans and never forget the sacrifices that they have made on behalf of our country and our freedoms.

April 16, 1996

Statement of Rep. Lane Evans
Subcommittee on Hospital and Health Care

Mr. Chairman, thank you for holding this hearing on the latest report by the National Academy of Sciences' Institute of Medicine on Agent Orange exposure.

The report confirms what Vietnam veterans have known all along - that Agent Orange has and will continue to exact a high price on themselves and their families. In particular, the finding that there is a limited /suggestive evidence of an association between Agent Orange exposure to vets and the occurrence of Spina Bifida in their children raises a number of questions of how our government must respond.

I believe we must now take action as we have in the past with respect to veterans who suffered from conditions in the "second tier" of the NAS report. The children of these vets deserve and should receive the proper health care and compensation for an affliction that was due to service to our nation.

I applaud Secretary Brown's quick action on this matter. I hope that the task force he named that we will hear from today concludes its work quickly and effectively. It is my understanding that it will be primarily examining the science behind the NAS report. This must be done, and I'm sure that much more work will be conducted in the future to better understand dioxin and its relationship to birth defects. However, the bottom line is that we have sick children who have paid the price because of their father's service to our nation. They need and deserve the best that our nation can give them. I hope that this is the same conclusion that the VA comes to at the end of their review.

Today should just be the beginning of the Committee's work on this issue. I hope in the near future we can hear from the veterans and their families, along with the service providers who assist them in coping with Spina Bifida, so we can get a first-hand look at the debilitating and extensive nature of this condition. The Secretary's Task Force should do the same. Without their input, our response to this latest chapter in the troubling legacy of Agent Orange will be clearly inadequate.

Mr. Chairman, again thank you for convening this hearing and I look forward to working with you on this issue in the future.

VETERANS AND AGENT ORANGE: UPDATE 1996
FINDINGS REGARDING SPINA BIFIDA AND OTHER HEALTH EFFECTS OF EXPOSURE TO AGENT ORANGE OR DIOXIN

Statement of

David Tollerud, MD, MPH
Chair, Committee to Review the Health Effects
in Vietnam Veterans of Exposure to Herbicides
and
Associate Professor and Chief, Division of Occupational and Environmental Medicine
University of Pittsburgh

and

Andrew Olshan, PhD
Member, Committee to Review the Health Effects
in Vietnam Veterans of Exposure to Herbicides
and
Assistant Professor, Department of Epidemiology, School of Public Health
University of North Carolina at Chapel Hill

representing the
Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides
Institute of Medicine

before the
Subcommittee on Hospitals and Health Care
Committee on Veterans' Affairs
U.S. House of Representatives

April 16, 1996

Good morning, Mr. Chairman and members of the Committee. My name is David Tollerud. I am Associate Professor and Chief of the Division of Occupational and Environmental Medicine at the University of Pittsburgh. I was the chair of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. This Committee was organized under the auspices of the Institute of Medicine, a private, non-profit organization that provides health policy advice under a congressional charter granted to the National Academy of Sciences.

I will begin by briefly explaining the intent of the report written by our committee, and reviewing its major findings. Dr. Andrew Olshan, a member of the committee with specific expertise in reproductive health effects, will then go into more detail regarding the findings on spina bifida and other reproductive outcomes.

For Vietnam veterans and their families, the issue of Agent Orange exposure has been a source of great anguish. To address these concerns, Congress passed the Agent Orange Act of 1991, which directed the Secretary of Veterans Affairs to request the National Academy of Sciences to do an independent, comprehensive review and critical evaluation of the scientific studies and medical evidence concerning the health effects of herbicide exposure.

The goal of the first study, which was also conducted by a committee of the Institute of Medicine, was to establish an agreed-upon base of information from which to proceed to answer specific questions. For each disease, the committee was asked to determine, to the extent that available data permitted meaningful determinations: 1) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association; 2) the increased risk of the disease among those exposed to herbicides during Vietnam service; and 3) whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

The Agent Orange Act also specified that this information base should be updated every two years. The information we are discussing today was developed for the first update of that report, which incorporates new scientific information that has become available since the initial study. As part of our testimony, we are submitting a copy of the Executive Summary of the report which we ask to be included in the record.

The committee studied both the toxicological and the epidemiologic data on herbicide exposures. After reviewing a large number of studies, we focused on approximately 35 new epidemiologic investigations for detailed review and analysis. Most of these studies were of people who were exposed to herbicides or dioxin as a result of their jobs or as a result of contact in the environment — for example, because of a nearby industrial accident. However, as Dr. Olshan will detail, the information on reproductive health effects came primarily from studies of Vietnam veterans. I should emphasize that the committee's analysis was limited to the types of herbicides used in Vietnam, and the contaminant dioxin.

In conducting its study, the committee operated independently of the Department of Veterans Affairs and other government agencies. It was not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. The committee was charged with reviewing the scientific evidence rather than making recommendations regarding policy, and the committee's findings are not intended to imply or suggest any policy decisions; these must rest with the government. Instead, the study provides scientific information for the Secretary of Veterans Affairs and others to consider as they exercise their responsibilities to Vietnam veterans.

The committee classified diseases into four categories, following the form of the first report: the first category shows "sufficient evidence" of a statistical association between the disease and exposure to herbicides or dioxin; in the second category, there was "limited or suggestive evidence"; in the third category, there was "inadequate or insufficient" evidence to determine whether an association exists; and in the fourth category, there was "limited, suggestive evidence of *no* association." Consistent with the mandate of the Agent Orange Act, the distinctions between categories are based on *statistical association*, not on *causality*. As a result, the committee did not apply the standard criteria epidemiologists use when judging whether a causal relationship exists between an exposure and a health outcome. The findings in the *1996 Update* are based on all of the available information, but the analysis concentrates on new evidence published since the first report.

Based on these evaluations, the committee found sufficient evidence of a statistical association between exposure to herbicides or dioxin and three types of cancer: soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. We also found sufficient evidence of an

association with chloracne, a skin condition. There is no change in the committee's findings about these outcomes from the earlier report.

The committee found limited or suggestive evidence of an association between exposure to herbicides or dioxin and three other types of cancer: respiratory cancers, prostate cancer, and multiple myeloma. The results for these cancers also did not change from the 1994 report.

The committee identified two new health effects in the category of limited or suggestive evidence of an association between herbicide or dioxin exposure. One is the acute, transient form of peripheral neuropathy, a nerve disorder that can lead to pain, numbness, and weakness in the limbs.

The committee also found limited or suggestive evidence that herbicide or dioxin exposure may be associated with a congenital birth defect called spina bifida in the children of fathers who were exposed to herbicides. The results of three studies of Vietnam veterans suggest that a father's exposure to herbicides may put his children at a greater risk of spina bifida, which is characterized by a deformity of the spine and spinal cord and can cause neurological problems.

For most of the other cancers, diseases, and conditions reviewed by the committee, the scientific data were not sufficient to determine whether an association exists. These include a broad range of birth defects other than spina bifida.

The greatest problem that the committee encountered was a severe lack of information about the exposure of individual Vietnam veterans to herbicides. Except for particular groups, such as those involved in Operation Ranch Hand and other groups directly involved in spraying operations, information on the extent of herbicide exposure among veterans is practically non-existent. This lack of data is why we were compelled to focus largely on epidemiologic studies of groups *other* than Vietnam veterans. We simply do not know enough about the exposures of individual veterans to determine to what degree they were or are at risk. Although most veterans probably experienced lower levels of exposure than those who work with the chemicals over long periods in occupational or agricultural settings, it is difficult to determine precisely which veterans may have encountered higher levels.

The Institute of Medicine will continue to work with the Department of Veterans Affairs on this issue, especially in a recently initiated project on historical exposure reconstruction that follows up on the research recommendations in the 1994 report.

As we said when we issued the first report on veterans and Agent Orange, we know this report will not end the controversy. But we hope these additional findings will lead to better understanding of the questions that remain, and the steps we must take to answer them.

I would now like to ask Dr. Olshan to speak with you about the committee's findings on the association between herbicide or dioxin exposure and adverse reproductive outcomes.

Good morning, Mr. Chairman and members of the Committee. My name is Andrew Olshan and I am Assistant Professor of Epidemiology at the School of Public Health of the University of North Carolina at Chapel Hill.

One of the tasks of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides was to review the published scientific literature on exposure to herbicides and adverse reproductive and developmental effects, focusing on studies published since the 1994 *Veterans and Agent Orange* report. This literature included a number of studies that evaluated herbicide exposure and the risk of adverse outcomes, including miscarriages, birth defects, stillbirths, neonatal and infant mortality, low birthweight, and sperm quality and infertility.

The primary emphasis of the original report and the present review is on the potential adverse reproductive and developmental effects of herbicide exposure for males, because the vast majority of the Vietnam veterans are men.

The committee examined studies of reproductive problems of men exposed to herbicides or dioxin as a result of their occupation, exposures in the environment, or their service in Vietnam. For many of the outcomes, there was inadequate or insufficient evidence to determine whether an association exists. These include altered sperm parameters, infertility, miscarriage, still birth, and cancer in their children.

The committee also closely examined studies regarding the occurrence of birth defects in the children of Vietnam veterans. The March of Dimes defines a birth defect as "an abnormality of structure, function or metabolism, whether genetically determined or as the result of an environmental influence during embryonic or fetal life." Major birth defects, which are usually defined as those abnormalities that are present at birth and severe enough to interfere with viability or physical well-being, are seen in approximately 2 to 3 percent of live births. Birth defects are detected in an additional 5 percent of children within the first year of life.

There is inadequate or insufficient information to determine whether an association exists between exposure to the herbicides or dioxin and most birth defects. However, recently published results of a study of the offspring of veterans who participated in the Operation Ranch Hands spraying program suggest the possibility of an association between dioxin exposure and risk of a particular group of birth defects collectively called neural tube defects. Anencephaly and spina bifida are two of the most common of the neural tube defects. Anencephaly is the congenital absence of a major portion of the brain, skull and scalp; it almost always results in death within the first week after birth. Spina bifida is an incomplete closure in the spinal column. The studies examined by the committee addressed the more severe of the major types of spina bifida, in which a portion of the spinal cord protrudes through the back at birth. This type is generally called "spina bifida cystica." Most infants born with spina bifida grow to adulthood with varying degrees of paralysis. In the general population in the U.S., spina bifida without anencephaly is seen in about 5 out of every 10,000 live births.

Some studies of veterans appear to show an elevated relative risk for either service in Vietnam or estimated exposure to herbicides or dioxin and neural tube defects in their offspring. On the basis of the pattern of findings in these studies, the committee concluded there was "limited or suggestive evidence" of an association between exposure to the herbicides or dioxin and spina bifida. For outcomes in this category, the evidence must be suggestive of an association with herbicides or dioxin, but limited because chance, bias, and confounding could not be ruled out with confidence. Typically, at least one high-quality study must indicate a positive association, although the results of other studies may be inconsistent.

For spina bifida, the committee gave particular attention to the results of three studies it found to be of high overall quality: The Ranch Hands Study, the Centers for Disease Control Birth Defects Study, and the CDC Vietnam Experience Study.

In the Ranch Hand study, spina bifida and anencephaly were increased among offspring of the veterans who were studied, with four total among 792 live births to Ranch Hands in contrast to none in a comparison group of 981 live births to Air Force veterans not involved in the spraying program. The Ranch Hand veterans were classified according to estimates of their dioxin exposure based on their blood levels of dioxin. Of the four infants with neural tube defects, two with spina bifida were born to fathers in the high dioxin level category; one with anencephaly and one with

spina bifida were born to fathers in the low dioxin category. The validation of self-reported birth defects in this study was systematic and of high quality, and the study controlled for an array of other factors.

The CDC Veterans Experience Study found that more Vietnam veterans reported that their children had a central nervous system anomaly than did non-Vietnam veterans. A substudy was conducted as an attempt to validate the reported defects — including spina bifida and anencephaly — by examination of hospital records. A difference was detected, but its interpretation was limited by various reporting and data validation problems.

The CDC Birth Defects Study utilized the population-based birth defects registry system in the metropolitan Atlanta area. There was no association between overall Vietnam veteran status and the risk of spina bifida or anencephaly. However, when an estimate of herbicide exposure opportunity based on self-reported dates and location of service was used in the analysis, there was an association between an increased risk of spina bifida and higher exposure potential. There was no similar pattern of association for anencephaly. This study has a number of strengths, including the use of a population-based birth defects registry system and the adjustment for a number of other factors that might have affected the risk of birth defects. Study limitations include the relatively low response rates among the individuals being surveyed, the time lag between birth and interview for some study participants, and imprecise exposure measurement.

Thus, taken as a group, these three epidemiologic studies suggest an association between herbicide exposure and an increased risk of spina bifida in offspring. Although the studies were judged to be of relatively high quality, they do suffer from methodologic limitations, including possible recall bias, nonresponse bias, small sample size, and misclassification of exposure and outcome. In addition, the failure to find a similar association with anencephaly, an embryologically-related defect, is of concern.

Thank you for your attention. Dr. Tollerud and I would be happy to answer your questions.

EXECUTIVE SUMMARY

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Veterans and Agent Orange: Update 1996

Committee to Review the Health Effects in
Vietnam Veterans of Exposure to Herbicides

Division of Health Promotion and
Disease Prevention

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine 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. In this, the Institute acts under the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logo-type by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemusseen in Berlin.

COMMITTEE TO REVIEW THE HEALTH EFFECTS IN VIETNAM VETERANS OF EXPOSURE TO HERBICIDES

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Preface

In response to the concerns voiced by Vietnam veterans and their families, Congress called upon the National Academy of Sciences (NAS) to review the scientific evidence on the possible health effects of exposure to Agent Orange and other herbicides (Public Law 102-4, signed on February 6, 1991). The creation of the first NAS Institute of Medicine committee, in 1992, underscored the critical importance of approaching these questions from a scientific standpoint. The original Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides realized from the beginning that it could not conduct a credible scientific review without a full understanding of the experiences and perspectives of veterans. Thus, to supplement its standard scientific process, the original committee opened several of its meetings to the public in order to allow veterans and other interested individuals to voice their concerns and opinions, to provide personal information about individual exposure to herbicides and associated health effects, and to educate the original committee on recent research results and studies still under way. This information provided a meaningful backdrop for the numerous scientific articles that the original committee reviewed and evaluated.

Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam (IOM, 1994) reviewed and evaluated the available scientific evidence regarding the association between exposure to dioxin or other chemical compounds contained in herbicides used in Vietnam and a wide range of health effects and provided the committee's findings to the Secretary of Veterans Affairs to consider as the Department of Veterans Affairs carried out its responsibilities to Vietnam veterans. The report also described areas in which the available scientific data were insufficient to determine whether an association exists and provided the committee's recommendations for future research.

Public Law 102-4 also asked the IOM to conduct biennial updates that would review newly published scientific literature regarding statistical associations between health outcomes and exposure to dioxin and other chemical compounds in these herbicides. The focus of this first updated review is on new scientific studies published since the release of *Veterans and Agent Orange (VAO)* and on updates of scientific studies previously reviewed in *VAO*. To conduct this

review, the IOM established a new committee of 16 members representing a wide range of expertise to take a fresh look at the studies reviewed in *VAO* and new scientific studies to determine whether an association exists between herbicide exposure and specific health outcomes. In order to provide a link to *VAO*, nearly half of the committee members had also served on the original committee. All committee members were selected because they are leading experts in their fields, have no conflicts of interest with regard to the matter under study, and have taken no public positions concerning the potential health effects of herbicides in Vietnam veterans or related aspects of herbicide or dioxin exposure. Biographical sketches of committee members and staff appear in Appendix C.

The committee worked on several fronts in conducting this updated review, always with the goal of seeking the most accurate information and advice from the widest possible range of knowledgeable sources. Consistent with procedures of the IOM, the committee met in a series of closed sessions and working group meetings in which members could freely examine, characterize, and weigh the strengths and limitations of the evidence. Given the nature of the controversy surrounding this issue, the committee deemed it vital to convene an open meeting as well. The public meeting was held in conjunction with the committee's first meeting, in April 1995, and provided the opportunity for veterans and veterans service organizations, researchers, policymakers, and other interested parties to present their concerns, review their research, and exchange information directly with committee members. To solicit broad participation, the committee sent announcements to nearly 1,300 individuals and organizations known to have an interest in this issue. The oral presentations and written statements submitted to the committee are described in detail in Appendix A.

In addition to its formal meetings, the committee actively and continuously sought information from, and explained its mission to, a broad array of individuals and organizations with interest or expertise in assessing the effects of exposure to herbicides. These interactions included meetings with representatives of veterans service organizations, congressional committees, federal agencies, and scientific organizations. The committee also heard from the public through telephone calls and letters, each of which received a response from the IOM staff.

Most of the committee's work involved reviewing the scientific literature bearing on the association between herbicides or dioxin and various health outcomes. The literature included studies of people exposed in occupational and environmental settings to the types of herbicides used in Vietnam, as well as studies of Vietnam veterans. The committee reviewed the original publications themselves rather than summaries or commentaries. Such secondary sources were used to check the completeness of the review. The committee also reviewed the primary and secondary literature on basic toxicological and animal studies related to dioxin and other herbicides in question.

As explained in the Executive Summary on page 12, the committee found that, in general, it is not possible to quantify the degree of risk likely to be experienced by Vietnam veterans because of their exposure to herbicides in Vietnam. Two members of the committee believe that there are certain circumstances under which the risk to veterans can be quantified. Appendix B presents their analysis and estimates; it represents their opinion alone.

Kelley Brix served as the original study director for this project and deserves credit for drafting sections of the report. The committee would also like to acknowledge the excellent work of the staff members, David Butler, Deborah Katz, and Amy Noel O'Hara. The committee would also like to thank Michael Stoto, Cynthia Abel, and Diane Mundt, who also served as staff members

for the original committee; their knowledge of the subject was helpful in completing the report. Thanks are also extended to Mona Brinegar, who handled the finances for the project; Thomas Burroughs, who provided excellent editorial skills; Michael Edington, who supervised the report through the editorial and publication phases; and Donna Thompson, who provided assistance with editorial changes to the manuscript.

David Tollerud, *Chairman*

Contents

1

Executive Summary

Because of continuing uncertainty about the long-term health effects of exposure to herbicides used in Vietnam, Congress passed Public Law 102-4, the "Agent Orange Act of 1991." This legislation directed the Secretary of Veterans Affairs to request the National Academy of Sciences (NAS) to conduct a comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of these herbicides, including dioxin. The Institute of Medicine (IOM) of the NAS conducted this review and in 1994 published a comprehensive report, entitled *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam* (IOM, 1994).

Public Law 102-4 also called for the NAS to conduct subsequent reviews at least every two years for a period of ten years from the date of the first report. The NAS was instructed to to conduct a comprehensive review of the evidence that has become available since the previous IOM committee report; and reassess its determinations and estimates of statistical association, risk, and biological plausibility.

This IOM report presents the first updated review and evaluation of the newly published scientific evidence regarding associations between diseases and exposure to dioxin and other chemical compounds in herbicides used in Vietnam. For each disease, the IOM was asked to determine, to the extent that available data permitted meaningful determinations: 1) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association; 2) the increased risk of the disease among those exposed to herbicides during Vietnam service; and 3) whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease.

In addition to bringing the earlier scientific evidence up to date, the committee has addressed several specific areas of concern, as requested by the Department of Veterans Affairs (DVA). These are: 1) the relationship between exposure to herbicides and the development of acute and subacute peripheral neuropathy; 2) the relationship between exposure to herbicides and the development of

prostate cancer, hepatobiliary cancer, and nasopharyngeal cancer; and 3) the relationship between the length of time since first exposure and the possible risk of cancer development.

In conducting its study, the IOM committee operated independently of the DVA and other government agencies. The committee was not asked to and did not make judgments regarding specific cases in which individual Vietnam veterans have claimed injury from herbicide exposure. Rather, the study provides scientific information for the Secretary of Veterans Affairs to consider as the DVA exercises its responsibilities to Vietnam veterans.

ORGANIZATION AND FRAMEWORK

The conclusions in this updated report are based on cumulative evidence from the scientific literature reviewed in *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, which will be abbreviated here as *VAO*. This update is intended to supplement rather than replace *VAO*; therefore, most of the background information has not been repeated. Most chapter sections begin with brief summaries of the scientific data in *VAO*, followed by a more thorough discussion of the newly published data and their interpretation. The reader is referred to relevant sections of *VAO* for additional detail and explanation.

Chapter 2 provides an overview of the methods and conclusions *VAO*. In addition, it provides a summary of the recent activities of several federal government agencies that are relevant to the health effects of Agent Orange and other herbicides used in Vietnam. Chapter 3 provides an update of the recent experimental toxicology data on the effects of the herbicides and of TCDD, a compound found as a contaminant in the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). These data serve as the basis for the biological plausibility of potential health effects in human populations. Chapter 4 describes the methodological considerations that guided the committee's review and its of evaluation. Chapter 5 updates the exposure assessment issues in *VAO* Chapter 8 reviews the methods used to study latency, or time-related effects—a topic of special interest to the DVA—and evaluates the evidence on latency for the cancers under study.

The committee focused most of its efforts on reviewing and interpreting epidemiologic studies, in order to judge whether each of the human health effects is associated with exposure to herbicides or dioxin. The committee weighed the strengths and limitations of the scientific data in *VAO* as well as the newly published scientific data, and reached its conclusions by interpreting the new evidence in the context of the original report. In particular, each disease has been placed into one of four categories, depending on the strength of evidence for an association (see Conclusions about Health Outcomes, below). The committee used the same criteria to categorize diseases as were used in *VAO*.

In the chapters on the various health outcomes (7, 9, 10, and 11), the committee relied on many of the same epidemiologic studies when assessing the potential associations with herbicides. Therefore, Chapter 6 provides a framework for the methods used in the epidemiologic studies. The chapter is organized to reflect similarities and differences in the nature of exposure among three types of study populations: occupationally exposed, environmentally exposed, and Vietnam veterans.

TOXICOLOGY SUMMARY

Chapter 3 reviews the results of animal studies published during the past three years that investigated the toxicokinetics, mechanism of action, and disease outcomes of TCDD, plus the herbicides themselves.

TCDD elicits a diverse spectrum of biological sex-, strain-, age-, and species-specific effects, including carcinogenicity, immunotoxicity, reproductive/developmental toxicity, hepatotoxicity, neurotoxicity, chloracne, and loss of body weight. These effects vary according to the age, sex, species, and strain of the animals involved. To date, the scientific consensus is that TCDD is not genotoxic and that its ability to influence the carcinogenic process is mediated via epigenetic events such as enzyme induction, cell proliferation, apoptosis, and intracellular communication.

Recent studies on the effects of TCDD and related substances on the immune system amplify earlier findings and suggest that these compounds affect primarily the T-cell arm of the immune response. Direct effects of TCDD on T cells in vitro, however, have not been demonstrated suggesting that the action of TCDD may be indirect. In contrast, a number of animal studies of the reproductive and developmental toxicity of TCDD suggests that developing animals may be particularly sensitive to the effects of TCDD. Specifically, male reproductive function has been reported to be altered following perinatal exposure to TCDD. In addition, experimental studies of the effects of TCDD in the peripheral nervous system suggest that TCDD can cause a toxic polyneuropathy in rats after a single, low dose. Other recent studies provide evidence that hepatotoxicity of TCDD involves AhR-dependent mechanisms.

The most recent studies have focused on the elucidation of the molecular mechanism of TCDD toxicity. The evidence further supports to the concept that the toxic effects of TCDD involve AhR-dependent mechanisms. A better appreciation of the complexity of TCDD effects in target cells has led to the development of refined, physiologically based pharmacokinetic models. These models take into account intracellular diffusion, receptor and protein binding, and liver induction to establish the fractional distribution of the total body burden as a function of the overall body concentration. The association of TCDD with the cytosolic AhR has been shown to require a second protein, known as ARNT, for DNA binding capability and transcriptional activation of target genes. There is also increasing evidence suggesting that events other than receptor binding influence biological response to TCDD. It is now clear that AhR-related signaling influences, and is itself influenced by, other signal transduction mechanisms at low concentrations. Signaling interactions explaining the toxic effects of TCDD may involve growth factors, free radicals, the interaction of TCDD with the estrogen transduction pathway, and protein kinases.

The toxicity of the herbicides used in Vietnam remains poorly studied. In general, the herbicides 2,4-D, 2,4,5-T, cacodylic acid, and picloram have not been identified as particularly toxic substances since high concentrations are often required to modulate cellular and biochemical processes. Impairment of motor function has been reported in rats administered high single oral doses of 2,4-D. The ability of 2,4,5-T to interfere with calcium homeostasis in vitro has been documented and linked to the teratogenic effects of 2,4,5-T on the early development of sea urchin eggs. There is evidence suggesting that both 2,4-D and 2,4,5-T are capable of inducing renal lesions in rats. A series of studies indicates that high concentrations of cacodylic acid results in the formation of a toxic intermediate, the dimethylarsenic radical. No recent studies pertaining to the toxicity of picloram have been published. The half-life in the body of 2,4-D and 2,4,5-T is relatively short and does not appear to extend beyond two weeks. 2,4-D binds covalently to hepatic proteins and lipids, but the molecular basis of this interaction and its biologic consequences are unknown.

EXPOSURE ASSESSMENT

Assessment of individual exposure to herbicides and dioxin is a key element in determining whether specific health outcomes are linked to these compounds. The committee has found, however, that the definition and quantification of exposure are the weakest methodologic aspects of the epidemiologic studies. Although different approaches have been used to estimate exposure among Vietnam veterans and among various occupationally and environmentally exposed groups, each approach is limited in its ability to determine precisely the intensity and duration of individual exposure.

Since the publication of *VAO*, there has been considerable progress in the use of serum TCDD levels and/or quantitative exposure indices, as summarized in Chapter 5. There also has been progress in characterizing the TCDD body burdens in several groups, including the Ranch Hand cohort, Seveso residents, German herbicide production employees, and Vietnamese civilians (Michalek, et al., 1996; Needham, et al., 1994; Flesh-Janys, et al., 1994; Ott, et al., 1993; and Verger, et al., 1994). The mean half-life of TCDD in humans has been calculated to be about 8.7 years in the Ranch Hand cohort (Michalek, et al., 1996). Serum TCDD measurements may provide valuable information about past herbicide exposure under some conditions, and they are best used to detect differences in exposure levels among large groups in epidemiologic studies. This additional information on TCDD body burdens in specific groups and information on half-lives allow more accurate comparisons of relative levels of exposure to TCDD among cohorts.

Although definitive data are lacking, the available evidence suggests that Vietnam veterans as a group had substantially lower exposure to herbicides and dioxin than did the subjects in many occupational studies. The participants in Operation Ranch Hand and the Army Chemical Corps are exceptions to this pattern, and it is likely that there are others who served in Vietnam who had exposures comparable in intensity to members of the occupationally exposed cohorts. It is currently not possible to identify this heavily exposed fraction of Vietnam veterans, although exposure reconstruction methods with this capability could perhaps be developed and validated.

CONCLUSIONS ABOUT HEALTH OUTCOMES

Chapters 7, 9, 10, and 11 provide a detailed evaluation of the epidemiologic studies reviewed by the committee and their implications for cancer, reproductive effects, neurobehavioral effects, and other health effects. As is detailed in Chapter 4, the committee used the epidemiologic evidence it reviewed to assign each of the health outcomes being studied into one of the four categories listed in Table 1-1. The definitions of the categories and the criteria for assigning a particular health outcome to them are described in the table, and the specific rationale for each of the findings is detailed in Chapters 7, 9, 10 and 11.

Consistent with the mandate of Public Law 102-4, the distinctions between categories are based on "statistical association," not on causality, as is common in scientific reviews. Thus, standard criteria used in epidemiology for assessing causality (Hill, 1971) do not strictly apply. The committee was charged with reviewing the scientific evidence rather than making recommendations regarding DVA policy, and Table 1-1 is not intended to imply or suggest any policy decisions; these must rest with the Secretary of Veterans Affairs.

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

Sufficient Evidence of an Association

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

Soft-tissue sarcoma
Non-Hodgkin's lymphoma
Hodgkin's disease
Chloracne

Limited/Suggestive Evidence of an Association

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

Respiratory cancers (lung, larynx, trachea)
Prostate cancer
Multiple myeloma
Acute and subacute peripheral neuropathy (new disease category)
Spina bifida (new disease category)
Porphyria cutanea tarda (category change in 1996)

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

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

Hepatobiliary cancers
Nasal/nasopharyngeal cancer
Bone cancer
Female reproductive cancers (cervical, uterine, ovarian)
Breast cancer
Renal cancer
Testicular cancer
Leukemia
Spontaneous abortion

Continued

TABLE 1-1 (continued)

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

Birth defects (other than spina bifida)
Neonatal/infant death and stillbirths
Low birthweight
Childhood cancer in offspring
Abnormal sperm parameters and infertility
Cognitive and neuropsychiatric disorders
Motor/coordination dysfunction
Chronic peripheral nervous system disorders
Metabolic and digestive disorders (diabetes, changes in liver enzymes, lipid abnormalities, ulcers)
Immune system disorders (immune suppression and autoimmunity)
Circulatory disorders
Respiratory disorders
Skin cancer (category change in 1996)

Limited/Suggestive Evidence of No Association

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

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

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

Health Outcomes with Sufficient Evidence of an Association

In *VAO*, the committee found sufficient evidence of an association with herbicides and/or TCDD for five diseases: soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, chloracne, and porphyria cutanea tarda (in genetically susceptible individuals). The recent scientific literature continues to support the classification of the first four of these diseases in the category of sufficient evidence. Based on the recent literature, the committee has reclassified porphyria cutanea tarda into the category of limited/suggestive evidence, as described below. Based on the recent literature, there are no additional diseases that satisfy this category's criteria—that a positive association between herbicides and the outcome must be observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. The committee regards evidence from several small studies that are free from bias and confounding, and that show an association that is consistent in magnitude and direction, as sufficient evidence for an association. The evidence that supports the committee's conclusions for the three cancers is detailed in Chapter 7 for chloracne in Chapter 11.

Health Outcomes with Limited/Suggestive Evidence of Association

In *VAO*, the committee found limited/suggestive evidence of an association for three cancers: respiratory cancer, prostate cancer, and multiple myeloma. The recent scientific literature continues to support the classification of these diseases in the category of limited/suggestive evidence. The literature also indicates that three additional conditions satisfy the criteria necessary for this category: spina bifida, acute and subacute (transient) peripheral neuropathy, and porphyria cutanea tarda (PCT). For outcomes in this category, the evidence must be suggestive of an association with herbicides, but the association may be limited because chance, bias, or confounding could not be ruled out with confidence. Typically, at least one high-quality study indicates a positive association, but the results of other studies may be inconsistent.

The evidence that supports the committee's conclusions for respiratory cancer and multiple myeloma is detailed in Chapter 7 and is not substantially changed from *VAO*. Because prostate cancer is one of the three cancer types of special interest to the DVA, a brief summary of the relevant scientific evidence is provided here. Because spina bifida, acute and subacute (transient) peripheral neuropathy, and porphyria cutanea tarda have been classified in the category of limited/suggestive since *VAO*, evidence for these associations is also provided.

Several studies have shown an elevated risk for prostate cancer in agricultural or forestry workers. In a large cohort study of Canadian farmers (Morrison, et al., 1993), an elevated risk of prostate cancer was associated with herbicide spraying, and the risk increased with increasing number of acres sprayed. The proportionate mortality from prostate cancer was elevated in a study of USDA forest conservationists (PMR = 1.6, CI 0.9-3.0) (Alavanja et al., 1989), and a case-control study of white male Iowans who died of prostate cancer (Burmeister et al., 1983) found a significant association with farming (OR = 1.2) that was not associated with any particular agricultural practice. These results are strengthened by a consistent pattern of nonsignificant elevated risks in studies of chemical production workers, agricultural workers, pesticide applicators, paper and pulp workers, and the population of Seveso, Italy. The largest recent study demonstrated a significantly increased

risk of death from prostate cancer in both white and nonwhite farmers in 22 of the 23 states that were studied (Blair et al., 1993). Studies of prostate cancer among Vietnam veterans or among people who have been exposed environmentally, have not consistently shown an association. However, prostate cancer is generally a disease of older men, and the risk among Vietnam veterans would not be detectable in today's epidemiologic studies. Because there was a strong indication of a dose-response relationship in one study (Morrison et al., 1993) and a consistent positive association in a number of others, the committee felt that the evidence for association with herbicide exposure was limited/suggestive for prostate cancer.

There have been three epidemiologic studies that suggest an association between paternal herbicide exposure and an increased risk of spina bifida. In the Ranch Hand study (Wolfe et al., 1995), neural tube defects (spina bifida, anencephaly) were increased among offspring of Ranch Hands with four total (rate of 5 per 1,000), in contrast to none among the comparison infants (exact p=.04). The Centers for Disease Control and Prevention (CDC) VES cohort study (Centers for Disease Control, 1989) found that more Vietnam veterans reported that their children had a central nervous system anomaly (OR=2.3; 95% CI 1.2-4.5) than did non-Vietnam veterans. The odds ratio for spina bifida was 1.7 (CI 0.6-5.0). In a substudy, hospital records were examined in an attempt to validate the reported cerebrospinal defects (spina bifida, anencephaly, hydrocephalus). While a difference was detected, its interpretation is limited by differential participation between the veteran groups and failure to validate negatives reported; that is, the veterans not reporting their children having a birth defect. Thus, the issue of a recall bias is of major concern with this study. In the CDC Birth Defects Study which utilized the population-based birth defects registry system in the metropolitan Atlanta area (Erickson et al., 1984), there was no association between Vietnam veteran status and the risk of spina bifida (OR=1.1, CI 0.6-1.7) or anencephaly (OR=0.9, CI 0.5-1.7).

However, the exposure opportunity index (EOI) based upon interview data was associated with an increased risk of spina bifida; for the highest estimated level of exposure (EOI-5) the OR was 2.7 (CI 1.2-6.2). There was no similar pattern of association for anencephaly. Thus, all three epidemiologic studies (Ranch Hand, VES, CDC Birth Defects Study) suggest an association between herbicide exposure and an increased risk of spina bifida in offspring. In contrast to most other diseases, for which the strongest data have been from occupationally exposed workers, these studies focused on Vietnam veterans. Although the studies were judged to be of relatively high quality, they suffer from methodologic limitations, including possible recall bias, nonresponse bias, small sample size, and misclassification of exposure. For these reasons, the committee concludes that there is limited/suggestive evidence for an association between exposure to herbicides used in Vietnam and spina bifida in offspring.

There is also limited/suggestive evidence of an association between exposure to herbicides and acute and subacute (transient) peripheral neuropathy. There are several published studies relevant to this health outcome, but they are primarily case histories from occupational studies and chemical reports following the Seveso accident, which describe transient symptoms of peripheral neuropathies in highly exposed intervals (Todd, 1962; Berkley and Nagle, 1963; Goldstein et al., 1959; Boeri et al., 1978; Pocchiaari et al., 1979; Filippini et al., 1981). Todd (1962) reported a sprayer of 2,4-D weedkiller who developed a gastrointestinal disturbance and, within days, after contact with the chemical, a severe sensory/motor polyneuropathy. Recovery occurred over a period of months. Berkley and Magee (1963) reported another patient who developed a polyneuropathy four days after exposure to a liquid solution of 2,4-D, which was being sprayed in a cornfield. The neuropathy was purely sensory in type. The patient's symptoms gradually resolved over months. Goldstein et al. described three patients with sensory/motor polyneuropathies that developed over

several days and progressed over several weeks after exposure to 2,4-D. All had incomplete recovery after several years. Although these patients were not examined neurologically before their exposure, the temporal relationship between the development of their clinical deficit and the herbicide exposure was clearly documented in the study (1959). Nonetheless, the possibility that their occurrence was unrelated to the herbicide exposure and was due to other disorders such as idiopathic Guillain-Barre syndrome cannot be entirely excluded. The trend to recovery in the individual cases reported and the negative findings of many long-term follow-up studies of peripheral neuropathy suggest that if a peripheral neuropathy indeed develops, it resolves with time.

Case reports and animal studies led to the conclusion in *VAO* that porphyria cutanea tarda (PCT) was associated with TCDD or herbicide exposure in genetically predisposed individuals. However, three recent reports (Jung et al., 1994; Calvert et al., 1994; and Von Benner et al., 1994) failed to support this association. Two studies (Calvert et al., 1994, and Jung et al., 1994) included extensive analysis of porphyrin levels on 451 workers with demonstrated or potential exposure to herbicides and TCDD. The studies found no relationship between porphyrin levels and TCDD levels, and no excess of PCT in these cohorts. However, some workers had evidence of increased porphyrins in urine, suggesting that further investigation is warranted. These new reports, combined with the literature reviewed in *VAO*, led the committee to conclude that there is limited/suggestive evidence of an association between PCT and exposure to herbicides and/or TCDD.

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

The scientific data for the remainder of the cancers and other diseases reviewed by the committee were inadequate or insufficient to determine whether an association exists. For cancers in this category, the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding or have inadequate exposure assessment. This group includes hepatobiliary cancers, nasal/nasopharyngeal cancer, bone cancer, female reproductive cancers (cervical, uterine, ovarian), breast cancer, renal cancer, testicular cancer, leukemia, and skin cancer. The scientific evidence for each of these cancers is detailed in Chapter 7. Recent published studies contained enough evidence to warrant moving skin cancer from the limited/suggestive evidence of no association category to this categoty. The scientific evidence for two cancers that are of special interest to the DVA—hepatobiliary cancer and nasopharyngeal cancer—will also be summarized here. Because of its public health importance, breast cancer also receives attention.

Several reproductive effects are classified in this category, including spontaneous abortion, birth defects other than spina bifida, neonatal/infant death and stillbirths, low birthweight, childhood cancer in offspring, and abnormal sperm parameters and infertility. The scientific evidence for reproductive effects is detailed in Chapter 9. Neurobehavioral effects that are classified in this category include cognitive and neuropsychiatric disorders, motor/coordination dysfunction, and chronic peripheral nervous system disorders. The scientific evidence for these effects is detailed in Chapter 10. Other health effects that are classified in this category include metabolic and digestive disorders, immune system disorders, circulatory disorders, and respiratory disorders. The scientific evidence for these effects is detailed in Chapter 11.

On the whole, the estimated relative risks for skin cancer are fairly evenly distributed around the null, and in a number of studies the confidence intervals were relatively narrow. This conclusion

led the committee responsible for *VAO* to conclude that there was limited/suggestive evidence of no association between skin cancer and exposure to herbicides used in Vietnam. One other recent study (Lynge, 1993), however, found an excess risk of skin cancer. Based on four cases, a statistically significant increase in the risk of melanoma was observed in the subgroup of men who had been employed for at least one year, using a ten-year latency period (SIR=4.3, CI 1.2-10.9). However, no information is given about the risk in men with less than 10 years of latency and expected numbers for women are not reported so obserbed elevated risk in the men with 10+ years of latency cannot be put into context. Another study found a significant excess risk in men from the Seveso area (SMR = 3.3), based on only three cases (Bertazzi et al., 1989a,b). The committee felt that these results, while not even suggestive evidence about an association, undermined the evidence of no association in *VAO*, and thus warranted changing skin cancer to the "inadequate/insufficient evidence to determine whether an association exists" category.

There are relatively few occupational, environmental, and veterans studies of hepatobiliary cancer, and most of these are small in size and have not controlled for lifestyle-related factors. The estimated relative risk in the various studies range from 0.3 to 3.3, usually with broad confidence intervals. Given the methodological difficulties associated with most of these studies, the evidence regarding hepatobiliary cancer is not convincing with regard to either an association or lack of association with herbicides or TCDD. The few studies that have been published since *VAO* (Asp et al., 1994; Bertazzi et al., 1993; Blair et al., 1993; Collins et al., 1993; and Cordier et al., 1993) do not change the conclusion that there is inadequate evidence to determine whether an association exists between exposure to herbicides and hepatobiliary cancer.

There are only a few occupational studies, one environmental study, and one veterans study of nasal and/or nasopharyngeal cancer, including two recently published studies (Asp et al., 1994, and Bertazzi et al., 1993). The estimated relative risks in the various studies range from 0.6 to 6.7, usually with broad confidence intervals. Thus, there is inadequate/insufficient evidence to determine whether an association exists between exposure to herbicides and nasal/nasopharyngeal cancer.

There have been a few occupational studies, two environmental studies, and two veterans studies of breast cancer among women exposed to herbicides and/or TCDD. These include four recently published studies (Bertazzi et al., 1993; Blair et al., 1993; Dalager et al., 1995; and Kogevinas et al., 1993). Most of these studies reported a relative risk of approximately 1.0 or less, but it is uncertain whether or not the female members of these cohorts had substantial chemical exposure. TCDD appears to exert a protective effect on the incidence of mammary tumors in experimental animals (see Chapter 3), which is consistent with the tendency for the relative risks to be less than 1.0. In summary, however, the committee believes that there is insufficient evidence to determine whether an association exists between exposure to herbicides and breast cancer.

Health Outcomes with Limited/Suggestive Evidence of No Association

In *VAO*, the committee found a sufficient number and variety of well-designed studies to conclude that there is limited/suggestive evidence of no association between a small group of cancers and exposure to TCDD or herbicides. This group includes gastrointestinal tumors (colon, rectal, stomach, and pancreatic), brain tumors, and bladder cancer. The recent scientific evidence continues to support the classification of these cancers in this category, and it is detailed in Chapter 7. Based

on the recent literature, there are no additional diseases that satisfy the criteria necessary for this category.

For outcomes in this category, several adequate studies covering the full range of levels of herbicide exposure that human beings are known to encounter are mutually consistent in not showing a positive association between exposure and health risk at any level of exposure. These studies have relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

The Relationship between the Length of Time Since Exposure and the Possible Risk of Cancer Development

The importance of latency effects and other time-related factors in determining cancer risk has long been recognized, and statistical methodologies have been developed to study this issue. A variety of practical difficulties relating to exposure assessment and other data requirements, however, have limited the use of these methods in epidemiological studies of environmental carcinogens. In response to the request from the DVA to explore latency issues related to herbicides used in Vietnam, the committee attempts in Chapter 8 to establish a methodology to address the timing of herbicide exposure and the risk of cancer. This chapter also reviews the literature on herbicide exposure and cancers classified in the "Sufficient Evidence of an Association" and "Limited/Suggestive Evidence of an Association" categories for results that describe how timing of exposure affects the relative risk due to exposure.

For four of the cancers studied—soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma—the committee concluded that there was not enough information in the literature about the timing of exposure and subsequent risk to further discuss latency issues. The committee did find that there was enough information about the timing of exposure and respiratory and prostate cancers, with considerably more information about the former than the latter, to warrant analysis of results. Both of these cancers are in the "Limited/Suggestive Evidence of an Association" category, and this conclusion has not changed after this investigation of time-related factors.

The evidence in the literature suggests that the time from exposure to TCDD to increased risk of respiratory cancer is less than ten years, and that the increase in relative risk continues for somewhat more than 20 years. The available literature does not indicate how long it takes for relative risks to return to one. These conclusions are based primarily on the study conducted by the National Institute for Occupational Safety and Health (Fingerhut, 1991), since this study is the most informative about the changes in risk of respiratory cancer with time since first exposure to TCDD, but the calculations are supported by other studies that have investigated time-related effects. The epidemiological literature was not informative on the effect of the age at which the exposure was received, or whether the carcinogen appeared to act at an early or late stage of the carcinogenic process.

The limited data do not indicate any increase in the relative risk of prostate cancer with time since exposure to TCDD. For prostate cancer, the epidemiological literature was not informative on how long the effects of exposure last, the effect of the age at which the exposure was received, or whether the carcinogen acts at an early or late stage of the carcinogenic process.

Increased Risk of Disease in Vietnam Veterans

Although there have been numerous health studies of Vietnam veterans, most have been hampered by relatively poor measures of exposure to herbicides or TCDD, in addition to other methodological problems. Most of the evidence on which the findings in Table 1-1 are based comes from studies of people exposed to dioxin or herbicides in occupational and environmental settings, rather than from studies of Vietnam veterans. The committee found this body of evidence sufficient for reaching the conclusions about statistical associations between herbicides and the health outcomes summarized in Table 1-1; however, the lack of adequate data on Vietnam veterans per se complicates the second part of the committee's charge, which is to determine the increased risk of disease among individuals exposed to herbicides during service in Vietnam. Given the large uncertainties that remain about the magnitude of potential risk from exposure to herbicides in the epidemiologic studies that have been reviewed (Chapters 7, 9, 10, and 11), the inadequate control for important confounders, and the uncertainty about the nature and magnitude of exposure to herbicides in Vietnam (Chapter 5), the necessary information to undertake a quantitative risk assessment is lacking. Thus, in general, it is not possible for the committee to quantify the degree of risk likely to be experienced by veterans because of their exposure to herbicides in Vietnam. The quantitative and qualitative evidence about herbicide exposure among various groups studied suggests that most Vietnam veterans (except for selected groups with documented high exposures, such as participants in Operation Ranch Hand) had lower exposure to herbicides and TCDD than the subjects in many occupational and environmental studies. However, individual veterans who had very high exposures to herbicides could have risks approaching those in the occupational and environmental studies.

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TESTIMONY OF

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NATIONAL CENTER FOR ENVIRONMENTAL HEALTH

BEFORE THE

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

COMMITTEE ON VETERANS' AFFAIRS

U.S. HOUSE OF REPRESENTATIVES

APRIL 16, 1996

Good morning. I'm Dr. Dave Erickson, Chief of the Birth Defects and Genetic Diseases Branch, National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC). I'm pleased to be here to provide testimony about CDC's two studies on birth defects among children fathered by veterans of the Vietnam conflict.

Major structural birth defects are common problems, affecting 3% or more of all babies. Birth defects are the leading cause of infant mortality, accounting for 20% of all deaths during infancy. If babies with birth defects survive, they usually require extensive and expensive surgical and medical care; in addition, many have lifelong disability. There are many different types of birth defects. One of the more serious and common specific kinds of defect is spina bifida, which is the focus of our discussions today. It is characterized by an improper formation of the vertebral column and spinal cord, as shown in the diagram attached to the last page of my prepared testimony. Babies born with spina bifida often survive, but they are usually affected by lower body paralysis and bowel and bladder incontinence. Anencephaly is a related malformation characterized by improper formation of the skull and brain, also shown in the attached diagram; babies born with anencephaly are either stillborn or die shortly after birth. Some babies are born with both spina bifida and anencephaly, and the two types of defects are thought to have at least some common causes.

CDC's first study, published in 1984, was based on data collected from families of babies born in the Metropolitan Atlanta area. Since 1967, CDC has gathered information on babies born with birth defects in the five-county area surrounding and including the city of Atlanta. This surveillance information identified about 5,000 families who had babies born from 1968 through 1980 with major structural birth defects. We then compared the percentage of fathers in this group who served in Vietnam with

the percentage among fathers of 3,000 babies who were born without birth defects. If Vietnam veterans in general had been at increased risk of having babies with birth defects, we would expect to find a higher proportion of Vietnam veterans among fathers of babies born with birth defects than among fathers of babies born without birth defects. What we found, however, was that 9.2% of fathers of babies with birth defects had served in Vietnam, compared to 9.5% of fathers of babies born without defects. Similarly, this study showed that Vietnam veterans in general were not at increased risk of fathering babies with spina bifida, or anencephaly.

At the time that the Atlanta study was done, there was no feasible laboratory method for measuring Vietnam veterans' exposure to the herbicide Agent Orange, or its suspected toxic contaminant, dioxin. Thus to try to evaluate the possible role of these compounds in the occurrence of birth defects in children of Vietnam veterans, we had to rely on other, less rigorous methods.

One of these methods was to ask each Vietnam veteran father whether he believed that he had been exposed to Agent Orange during his tour of duty in Vietnam. The answers showed that Vietnam veterans who thought that they had been exposed were no more likely to have had a baby affected by anencephaly or spina bifida than were Vietnam veterans who thought that they had not been exposed.

In another attempt to evaluate the possible connection between Agent Orange and birth defects, we constructed an index of opportunities for exposure to Agent Orange based on Vietnam veterans' military occupation and places and times of service in Vietnam; the scoring of individual veterans on the index was done by Department of Defense personnel. There was no association

between greater opportunities for exposure and the overall risk of fathering a baby with all types of birth defects combined. However, fathers who had greater opportunities for exposure, as estimated by our index, did have a statistically significant greater chance of fathering babies with spina bifida, although no such association was found for the related defect anencephaly. We found the association between spina bifida risk and fathers' scores on the Agent Orange exposure opportunity index noteworthy. But because of substantive uncertainties about the accuracy of the index, we were inclined to attribute the finding to chance. This inclination was strengthened by the lack of a parallel association with the related defect, anencephaly.

The second CDC study related to birth defects, the reproductive and child health component of the Vietnam Experience Study (VES), which was published in 1989, compared the rates of birth defects among babies fathered by about 7,900 Vietnam veterans with the rates among babies of 7,400 control veterans who did not serve in Vietnam. The veterans who participated in this study had all served in the Army, and came from all parts of the United States.

According to information obtained in telephone interviews with veterans, 6.5% of 12,788 babies fathered by Vietnam veterans had birth defects compared to 5.0% of 11,910 babies fathered by control veterans. Notable among the defects were anencephaly and spina bifida: they were reported in 0.09% babies of Vietnam veterans but in only 0.04% of babies of control veterans. Because of these findings, two substudies were added as components of the VES study: the General Birth Defects substudy, and the Cerebrospinal Malformations substudy.

The objective of the General Birth Defects substudy was to compare rates of total birth defects recorded on hospital birth records among children of veterans who served in Vietnam with

rates among children of veterans who did not. Records were collected for children of only a subset of participating veterans. According to these records, 7.3% of babies born to Vietnam veterans had a birth defect, compared with 7.1% of control veterans' babies; 2.9% of Vietnam veterans' babies had major malformations compared with 2.4% of control veterans' babies. No significant differences in spina bifida or anencephaly rates were noted in this substudy, but the number of affected babies was small. We believe that the results of this substudy indicate that Vietnam veterans were not at a general increased risk of fathering babies with defects. The higher rate of birth defects reported by Vietnam veterans during the interview phase of the study is thought likely due to differential reporting by Vietnam and control veterans and was not substantiated by review of objective hospital records.

In the Cerebrospinal Malformations substudy, hospital records were sought for a small subset of all babies reported to have been fathered by participating veterans. These were babies who, based on descriptions obtained in the interview, might be suspected of having spina bifida or anencephaly. This substudy was done to document from medical records cases of spina bifida and anencephaly reported by telephone interview and to locate additional cases that might not have been reported by veterans during their interviews. The search for unreported cases is considered important because many babies with spina bifida are stillborn, and parents may not have been adequately informed about the cause of the stillbirths. According to birth records, the Vietnam group and the control group each had four stillborn babies with spina bifida or anencephaly. Birth records also showed that Vietnam veterans had eight live born babies with spina bifida and seven with anencephaly, whereas control veterans had two live-born babies with spina bifida and three with anencephaly. A problem with this substudy, however, is that a veteran had to report that his baby had some sort of problem for

that baby's records to be included. Thus a veteran's baby about whom no problem was noted in the interview was not included in this substudy. While the number of babies verified as having been born with spina bifida or anencephaly was higher among Vietnam veterans than among control veterans, the number observed among Vietnam veterans' babies is consistent with national birth defects data, whereas the number among control veterans' babies is much lower. We have a number of reservations about these data, and an important limitation of the study was that it did not collect any information regarding potential exposure to Agent Orange. Nevertheless, it was interesting that both CDC studies had some potentially suggestive, albeit highly equivocal, findings relative to spina bifida.

You have heard already this morning about the results on spina bifida and anencephaly from the Air Force's Ranch Hand study. Even though these data have raised our interest further, the accumulative evidence is far from proving a cause and effect relationship between exposure to Agent Orange and spina bifida.

The causes of most birth defects are unknown, and more research is needed to identify causes so that these devastating problems can be prevented in the future. While we are at the present left with many questions about Vietnam veterans' risks for having babies with spina bifida, the past decade has witnessed a major breakthrough in our understanding of how a large fraction of spina bifida and anencephaly cases can be prevented. I want to close by telling you a bit about this research success story, and in particular about how CDC's Atlanta Vietnam veterans' birth defects study played a critical role in the establishment of the breakthrough.

In the CDC study, questions were included about maternal vitamin use in the interviews done for the Atlanta Vietnam veterans birth

defects study. Analysis of these vitamin use data showed that there was a much lower risk for having a spina bifida or anencephaly- affected pregnancy among women who consumed folic acid- containing vitamins. This finding was an important unexpected benefit of our Vietnam veterans birth defects study. As time went by, other research with similar findings accumulated.

We now know that if women consume 400 micrograms of the B-vitamin folic acid before conception and during early pregnancy, their risk for having a pregnancy affected by spina bifida or anencephaly can be cut in half. As a result, the Public Health Service recommends that all women of reproductive age should consume 400 micrograms of folic acid per day. Four hundred micrograms is the amount of folic acid that is found in most multivitamin pills. In a further unfolding of this tremendous prevention opportunity, the Food and Drug Administration has recently mandated the fortification of cereal grain flours with folic acid to help women reach the recommended level of consumption.

Although we have been unable to provide definitive answers about Vietnam veterans' risks for fathering babies with spina bifida, the studies conducted have contributed to the discovery of a tremendous prevention opportunity for spina bifida and anencephaly.

That concludes my testimony. Thank you for your attention. I will be happy to try to answer any questions you might have.

Spina bifida results from the failure of the spinal column to close. Most babies with this condition live but with disabling consequences which vary depending on the location of the open area on the spine. With severe spina bifida, a person's legs and feet are paralyzed, and there are problems with bowel and bladder control. Learning disabilities are common and mental retardation sometimes occurs.

Anencephaly is marked by the incomplete development of the skull bones and a partially or completely absent brain. Babies with anencephaly all die before birth or shortly thereafter.

DEPARTMENT OF THE AIR FORCE

PRESENTATION TO THE COMMITTEE ON VETERANS' AFFAIRS

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

UNITED STATES HOUSE OF REPRESENTATIVES

SUBJECT: HEALTH EFFECTS IN CHILDREN OF INDIVIDUALS EXPOSED TO AGENT ORANGE IN VIETNAM

STATEMENT OF: Dr. Joel E. Michalek, Ph.D.
Air Force Health Study Principal Investigator

April 16, 1996

NOT FOR PUBLICATION UNTIL RELEASED
BY THE COMMITTEE ON VETERANS' AFFAIRS
UNITED STATES HOUSE OF REPRESENTATIVES

Mr. Chairman and members of the committee, I am Joel Michalek, Principal Investigator of the Air Force Health Study, Armstrong Laboratory, Human Systems Center, Brooks Air Force Base, Texas. With me today is Colonel Gary Henriksen, a principal investigator of the study. I have prepared a brief introductory statement to bring you up to date regarding our work in reproductive outcomes and dioxin exposure in the Air Force Health Study.

The Air Force Health Study is a 20-year comprehensive assessment of the health, survival and reproductive outcomes of 1,098 Air Force veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of herbicides in Vietnam from 1962 to 1971. Ranch Hand veterans were exposed to dioxin during spray missions or by handling bulk quantities of Agent Orange and other herbicides. A comparison group of 1,549 Air Force veterans who also served in Southeast Asia during the same time period and who were not involved with spraying herbicides serves as a control group. Comparisons were matched to Ranch Hands on age, race and military occupation. All Ranch Hand veterans and comparisons are men. Physical examinations were performed and questionnaires were administered in 1982, 1985, 1987, and 1992. Additional examinations are planned for 1997 and 2002.

Reproductive experiences were assessed in the first Air Force Health Study report, released in 1984. The analyses of reproductive outcomes contained in that report were based on birth defects reported in 1982 by the mothers of the children. Those reports were not verified because the necessary medical records were not available at that time. Record retrieval and verification took place between 1985 and 1990. In 1982, 1985 and 1987, participants were asked to provide access to medical records documenting each conception and the health of each child through the age of 18. This task involved the collection of medical records on 9,921 conceptions, including 8,100 live births.

All reported conceptions and births were subjected to medical record verification. We verified the existence, lineage, and medical history through the age of 18 of 99.7 percent of

reported conceptions and 99.9 percent of reported births. The unverified outcomes were 20 aborted fetuses (five reported as spontaneous abortions and 15 terminated through induced abortions) and 10 liveborn infants.

During the same period, analytical chemists at the Centers for Disease Control and Prevention (CDC) developed an assay for dioxin in serum and demonstrated its suitability as a substitute for the assay of dioxin in adipose tissue obtained by biopsy. In 1987, blood from each willing participant was collected and assayed. Of the 995 Ranch Hands and 1,299 Comparison subjects who participated in the 1987 physical examination, 93.7 percent of the Ranch Hands and 92.5 percent of the Comparison subjects volunteered for the serum dioxin assay.

In 1990, we began analyzing verified reproductive outcomes versus paternal dioxin levels and exposure group. That first round of analyses concluded in 1991 and was summarized in 1992 in our first report of verified outcomes. That report included analyses of sperm counts and abnormalities, birth weight, miscarriages, abnormally low birth weight, birth defects, birth defect severity, developmental disabilities, and neonatal and infant mortality.

During the period 1992 through 1994, we updated our data files based on new information collected from the 1992 physical examination and reanalyzed birth defects, spontaneous abortions, stillbirths, birth defects, birth defect severity, delays in development and hyperkinetic activity, and, in collaboration with CDC, summarized the results in an article. The article was accepted for publication in 1994 and was published in 1995. That paper, entitled ``Paternal Dioxin and Reproductive Outcomes among Veterans of Operation Ranch Hand,'' is an attachment to this testimony.

To summarize the results of our birth defects study, we found no statistically or biologically meaningful elevation in risk for spontaneous abortion or stillbirth. (The term, ``biologically meaningful,'' indicates that there is scientific data or literature to support the validity of an association.) In analyses of birth defects, we found elevations in risk in some

organ system categories, which, after review of the clinical descriptions, were found to be not biologically meaningful. There was an increase in nervous system defects in Ranch Hand children with increased paternal dioxin, but it was based on sparse data. We found no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin. We concluded that these data provide little or no support for the theory that paternal exposure to Agent Orange and its dioxin contaminant is associated with adverse reproductive outcomes.

Between 1995 and the current date, we summarized abnormal follicle stimulating hormone, luteinizing hormone, and testosterone, testicular abnormalities, abnormally low sperm count, and abnormal sperm in an article to be published in July this year. Our analysis did not reveal a pattern of consistent or meaningful associations between dioxin body burden and follicle stimulating hormone, luteinizing hormone, testosterone or testicular abnormality. We assessed sperm abnormalities in morphology and count based upon lipid adjusted dioxin burden at the time of the collection of the semen sample. No exposed Ranch Hands met criteria for excessive abnormal sperm (30 percent or more) and no category of Ranch Hand personnel exhibited an increased risk of low sperm count (60 million per ml. or less).

As the Ranch Hand and Comparison veterans continue to have children, we periodically reanalyze the data to reassess all of these conditions versus paternal dioxin level and will continue to do so during the course of the study. Additionally, we have released the data files, without personal identifiers, on health and mortality of the study participants to the public, through the National Technical Information Service, Springfield, Virginia, and are preparing the reproductive outcome data for public release through the NTIS.

In conclusion, I want to make a few remarks about our findings on spine bifida. Our study identified three children with spine bifida born to Ranch Hand veterans, while none of the children of Comparison veterans had spine bifida. The three Ranch Hand fathers had elevated

serum dioxin levels. These results seem unusual, but the sparseness of the data limited our ability to assess the significance of the association. The Institute of Medicine has recently interpreted available evidence on spine bifida and exposure to herbicides as ``suggestive of an association'' but ``limited because chance, bias, and confounding could not be ruled out with confidence.'' The results of our study of Ranch Hand veterans and Comparisons were apparently important to the Institute of Medicine in reaching their conclusion. However, it is my opinion that the accumulated evidence does not yet establish that there is a cause-and-effect relationship between herbicide exposure and spine bifida.

Thank you for giving me the opportunity to be here today. I will be glad to answer any questions you may have about the study.

Paternal Serum Dioxin and Reproductive Outcomes among Veterans of Operation Ranch Hand

William H. Wolfe,[1] Joel E. Michalek,[1] Judson C. Miner,[1] Alton J. Rahe,[2] Cynthia A. Moore,[3] Larry L. Needham,[3] and Donald G. Patterson, Jr.[3]

We studied whether paternal exposure to Agent Orange and its dioxin contaminant (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) during the Vietnam War is related to adverse reproductive outcomes after service in Southeast Asia. The index cohort comprises conceptions and children of veterans of Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam from 1962 to 1971. The comparison cohort comprises conceptions and children of Air Force veterans who served in Southeast Asia during the same period but who were not involved with spraying herbicides. We found no meaningful elevation in risk for spontaneous abortion or stillbirth. In analyses of birth defects, we found elevations in risk in some organ system categories, which, after review of the clinical descriptions, were found to be not biologically meaningful. There was an increase in nervous system defects in Ranch Hand children with increased paternal dioxin, but it was based on sparse data. We found no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin. These data provide little or no support for the theory that paternal exposure to Agent Orange and its dioxin contaminant is associated with adverse reproductive outcomes. (Epidemiology 1995;6:17–22)

Keywords: dioxin, reproductive outcomes, cohort study.

The possibility of an increased risk of birth defects in children of Vietnam veterans has caused concern about dioxin exposure among veterans, the general public, and federal and state legislatures. To address these and other concerns, the Air Force began planning the Air Force Health Study in late 1978[1] to evaluate the health, survival, and reproductive experience of 1,098 Air Force veterans who regularly handled and sprayed dioxin-containing herbicides in Southeast Asia from 1962 to 1971. A comparison group of 1,549 Air Force veterans who also served in Southeast Asia during the same time period and who were not occupationally exposed to herbicides was included. Physical examinations were performed, and questionnaires were administered in 1982, 1985, 1987, and 1992. Additional examinations are planned for 1997 and 2002.

Reproductive experiences of the study cohorts were assessed in the first Air Force Health Study report, published in 1984.[2] The analyses of reproductive outcomes contained in that report were based on birth defects reported by the mothers of the children. Those reports were not verified because the necessary medical records were not available at that time. Attempts to locate and obtain records for each reported conception began in 1985. This task involved the collection of medical records on 9,921 conceptions, including 8,100 births. All reported conceptions and births, regardless of the biological relationship of the fetus or liveborn infant to the study participant or the time of conception relative to service in Southeast Asia, were subjected to medical record verification. We verified the existence, lineage, and medical history through the age of 18 of 9,891 of 9,921 reported conceptions (99.7%) and 8,090 of 8,100 reported births (99.9%). The 30 unverified outcomes were 20 aborted fetuses (5 reported as spontaneous abortions and 15 as terminated through induced abortions) and 10 liveborn infants.

Subjects and Methods

The details of the study design and subject selection have been published elsewhere.[3] In 1982, 1985,[4] and 1987,[5,6] participants, their wives, and other sexual partners were asked about the birth defect and mortality status of their children and about occurrences of stillbirths and abortions. Participation was voluntary, and consent forms were signed at the examination site. Parents were also asked to provide access to medical records documenting each conception and the health of each child through the age of 18. During the same period, analytical chemists at the Centers for Disease Control and Prevention (CDC) developed an assay for dioxin in serum[7] and demonstrated its suitability as a substitute for

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the assay of dioxin in adipose tissue obtained by biopsy.[8] In 1987, blood from each willing participant was collected and assayed. Of the 995 Ranch Hands and 1,299 comparison subjects who participated in the 1987 physical examination, 932 Ranch Hands (93.7%) and 1,202 comparison subjects (92.5%) volunteered for the dioxin assay.

This report summarizes analyses of associations between paternal serum dioxin levels and verified reproductive outcomes. All recognized pregnancies conceived during or after service in Southeast Asia by study participants with a quantifiable dioxin result were considered in these analyses.[9] Nine hundred thirty-two Ranch Hand veterans and 1,202 veterans from the comparison group had serum specimens analyzed by CDC before January 1990, when the databases for this report were prepared. Of these 932 Ranch Hand specimens, 20 were reported by CDC as below the limit of quantifiability, and 40 gave no result, owing to laboratory error; the reproductive outcomes of 872 Ranch Hands remained for consideration. Of the 1,202 veterans in the comparison group assayed for dioxin, we excluded the reproductive outcomes of 166 because the dioxin result was below the limit of quantifiability (N = 76) or missing due to laboratory error (N = 66), or because the dioxin level was greater than 10 parts per trillion (ppt), the level we regard as the upper threshold for background exposure (N = 24). The reproductive outcomes of 1,036 comparison veterans remained for consideration.

This report considers conceptions and children of veterans with a dioxin result conceived during or after the father's service in Southeast Asia. Hence, we excluded 1,628 conceptions and 1,298 children who were not fathered by study participants, 2,782 conceptions and 2,277 children who were fathered by study participants without a dioxin result, and 3,240 conceptions and 2,742 children fathered by study participants but conceived before the father's service in Southeast Asia, leaving 2,241 conceptions and 1,773 children eligible for inclusion in this study.

Of the 872 Ranch Hand veterans with dioxin results, 454 were responsible for 1,006 conceptions and 419 fathered 792 liveborn infants during or after service in Southeast Asia. Of the 1,036 comparison subjects with dioxin results, 570 were responsible for 1,235 conceptions, and 531 fathered 981 liveborn infants during or after service in Southeast Asia.

We stratified conceptions and children to four categories determined by paternal dioxin level (Table 1). We omitted the reproductive outcomes of comparison group veterans having current dioxin levels greater than 10 ppt because we suspect that the dioxin levels of some of these men may have become elevated subsequent to their service in Southeast Asia. One of the comparison subjects with an elevated dioxin level reported occupational exposure to industrial chemicals in the United States after his service in Vietnam. We did not attempt to assess post-Southeast Asia dioxin exposure in Ranch Hands.

TABLE 1. Numbers of Study participants, Conceptions, and Offspring by Dioxin Category

Dioxin Category	Definition*	Fathers	Conceptions	Liveborn Infants
Comparison	D ≤ 10	570	1,235	981
Ranch Hand				
Background	D ≤ 10	179	368	283
Low	10 < D & I ≤ 110	119	318	241
High	10 < D & I > 110	156	320	268
Total		1,024	2,241	1,773

* D = current dioxin; I = initial dioxin; in parts per trillion.

Offspring of comparison subjects having background levels serve as the referent group for Ranch Hand children. Reproductive outcomes of Ranch Hands having background dioxin levels (less than 10 ppt) constitute a separate stratum because the exposure status of the veterans in this category cannot be determined from current dioxin levels. Offspring of Ranch Hands with elevated dioxin levels (at least 10 ppt) were stratified to low and high categories, determined by the extrapolated initial dioxin level at the time of conception. The initial dioxin level was estimated using a first order decay rate model with a fixed 7.1-year half-life.[10] The cutpoint between the low and high categories (110 ppt) is the median initial dioxin level at the time of conception of reproductive outcomes of Ranch Hands with current dioxin levels greater than 10 ppt; the cutpoint has no biological meaning.

The time since exposure varies between 15 and 26 years, about 2 or 3 dioxin half-lives,[10] among Ranch Hands. The elimination of dioxin use in the intervening years and lack of alternative evidence of exposure leaves the exposure status of Ranch Hands having low current levels (below 10 ppt) unresolvable. The median dioxin level (6.1 ppt) in this subgroup, however, is slightly higher than that among comparison subjects at background levels (3.9 ppt), indicating that some of the Ranch Hands with low levels may have been exposed and their body burden decayed to less than 10 ppt, and some may not have been exposed at all. Hence, we regard this subgroup as a mixture of exposed and unexposed veterans, whose true status cannot be determined with available data.

We defined a spontaneous abortion as a spontaneous loss of an intrauterine pregnancy at less than 20 weeks gestation, and a stillbirth as a fetal death occurring at 20 weeks or greater gestation. We verified all conceptions, regardless of gestational period or outcome (induced or spontaneous abortion, stillbirth, livebirth), reported by study participants, their wives, or partners through the retrieval of medical documents and birth or death certificates. All retrieved records were independently reviewed for the identification and classification of anomalies and morbid conditions by two experienced medical record coders, blinded to the fathers' exposure status and dioxin levels. All conditions were classified in accordance with the rules and conventions of the *International*

Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).[11] In addition, all anomalies were independently reviewed by a clinical geneticist from CDC who was blinded to the fathers' exposure status and dioxin levels.

We verified birth defect status for liveborn infants and assigned birth defects to 13 categories defined by the CDC[12] (Table 2). When assessing associations between birth defects and dioxin, we did not include stillborn infants (N = 44); none of these had verifiable defects.

We defined major defects as those that could potentially affect survival, require substantial medical care, result in marked physical or psychological handicaps, or interfere with a child's prospects for a productive and fulfilling life. We classified other birth defects as minor or unspecified.[12]

In addition to the 13 categories of birth defects defined by CDC,[9] 12 specific birth defects (anencephaly, spina bifida, hydrocephalus, cleft palate, cleft lip/palate, esophageal atresia, anorectal atresia, hypospadias, congenital hip dislocation, polydactyly, limb reduction deformities, Down syndrome) and four developmental disabilities (disturbance of emotion specific to childhood and adolescence, hyperkinetic syndrome of childhood, specific delays in development, mental retardation) were also enumerated. We defined a liveborn infant as having multiple birth defects if he or she had two or more unrelated, serious, and specified birth defects of unknown etiology.

All analyses, except that of spontaneous abortion, were adjusted, via stratification, for six covariates: the father's race (black, nonblack), the mother's smoking during pregnancy (yes, no), the mother's drinking during pregnancy (yes, no), the mother's age at the time of the child's birth, the father's age at the time of the child's birth, and the father's military occupation in Southeast Asia (officer, enlisted flyer, enlisted nonflyer). We adjusted analyses of spontaneous abortion for these six covariates and, additionally, for the occurrence of spontaneous abortions before the father's service in Southeast Asia. The father's military occupation is a potential confounder because it is associated with dioxin level,[3] because most officers are college educated and most enlisted personnel are high school educated, and because education is generally associated with health.

Measures of congenital anomalies are, by definition, based upon prevalence at birth rather than true incidence,[13] even though the diagnosis may have occurred at any time up to age 18. In the analyses of spontaneous abortion, rates are expressed as the number of events per 1,000 recognized conceptions. In the analyses of birth defects, hyperkinetic syndrome, delays in development, and multiple birth defects, rates are expressed as the number of events per 1,000 liveborn infants.

TABLE 2. Birth Defect Category Definitions

Birth Defect Category	ICD-9-CM[11] Definition
Nervous system anomalies	740–742
Eye anomalies	743
Anomalies of the ear, face, and neck	744
Anomalies of the circulatory system and heart	745–747
Anomalies of the respiratory system	748
Anomalies of the digestive system	749–751
Genital system anomalies	752
Urinary system anomalies	753
Musculoskeletal system anomalies	754–756
Anomalies of the skin	757
Chromosomal anomalies	758
Other and unspecified anomalies	759
All anomalies	740–759

Results

Without regard to dioxin levels, there is no evidence to suggest that the ability of Ranch Hands to father conceptions is reduced relative to that of comparison subjects; 454 of 872 (52.1%) Ranch Hands and 570 of 1,036 (55.0%) comparison subjects fathered conceptions after service in Southeast Asia. Furthermore, there is no evidence of impaired ability among Ranch Hands to father children, given that they fathered a conception. The percentages of Ranch Hands and comparison subjects who fathered children, given that they fathered a conception, were 92.3% (419 of 454) and 93.2% (531 of 570).

Table 3 summarizes analyses of the association between dioxin and spontaneous abortion and stillbirth. There is an increased risk of spontaneous abortion in the background and low-dioxin categories, with the highest risk ratio (1.3) in the low category. There is an increased risk of stillbirth in the background and low-dioxin categories; the relative risk in both categories is 1.8. The small number of tubal pregnancies precluded a formal analysis.

The numbers of children with anomalies of the nervous (N = 8) and respiratory systems (N = 6) and the numbers of children with chromosomal anomalies (N = 7) and other unspecified anomalies (N = 5) were too small to permit analyses of association with paternal dioxin (Table 4). We found increased risk of birth defects in some organ system categories. For each organ

TABLE 3. Spontaneous Abortion, Stillbirth, and Tubal Pregnancy According to Paternal Dioxin Level among 454 Ranch Hand and 570 Comparison Subjects

Outcome	Comparison	Ranch Hand		
		Background	Low	High
Spontaneous abortion				
Number	172	57	56	44
RR*		1.1	1.3	1.0
95% CI		0.8–1.5	1.0–1.7	0.7–1.3
Stillbirth				
Number	13	7	6	1
RR		1.8	1.8	0.3
95% CI		0.7–4.5	0.7–4.7	0.0–2.3
Tubal pregnancy				
Number	7	1	2	0

* Denominators for risks are conceptions (Table 1).

TABLE 4. Birth Defects According to Paternal Dioxin Level among 454 Ranch Hands and 570 Comparison Subjects

Organ System	Comparison	Ranch Hand		
		Background	Low	High
Nervous system				
Number	3	0	2	3
Eye				
Number	7	4	2	3
RR*		2.0	1.2	1.6
95% CI		0.6–6.7	0.2–5.6	0.4–6.0
Ear, face, and neck				
Number	11	5	2	5
RR		1.6	0.7	1.7
95% CI		0.6–4.5	0.2–3.3	0.6–4.7
Circulatory system and heart				
Number	16	4	9	4
RR		0.9	2.3	0.9
95% CI		0.3–2.6	1.0–5.1	0.3–2.7
Respiratory system				
Number	2	2	0	2
Digestive system				
Number	24	6	7	5
RR		0.9	1.2	0.8
95% CI		0.4–2.1	0.5–2.7	0.3–2.0
Genital system				
Number	18	4	8	6
RR		0.2	1.8	1.2
95% CI		0.0–1.4	0.8–4.1	0.5–3.0
Urinary system				
Number	12	4	6	7
RR		1.2	2.0	2.1
95% CI		0.4–3.6	0.8–5.4	0.8–5.4
Musculoskeletal				
Number	132	34	34	31
RR		0.9	1.0	0.9
95% CI		0.6–1.3	0.7–1.5	0.6–1.2
Skin				
Number	21	5	7	3
RR		0.8	1.4	0.5
95% CI		0.3–2.2	0.6–3.2	0.2–1.7
Chromosomal anomalies				
Number	3	3	0	1
Other and unspecified				
Number	2	0	3	0
All anomalies				
Number	204	57	63	57
RR		1.0	1.3	1.0
95% CI		0.7–1.3	1.0–1.6	0.8–1.3

* Denominators for risks are liveborn infants (Table 1).

system category with increased relative risks in the low and/or high Ranch Hand groups, we reviewed the clinical description of the birth defects for similarity. Nine children born to fathers in the low-exposure group had circulatory system and heart defects. These defects [atrial septal defect (N = 3), transposition of the great vessels (N = 1), ventricular septal defect (N = 3), double outlet right ventricle (N = 1), and single umbilical artery (N = 1)] varied in type and pathogenesis. Eight children born to fathers in the low group had genital anomalies (2 with hypospadias, 4 with undescended testes, and 2 with vaginal tags). These defects were variably ascertained and showed no pattern or differences from the defects seen in the other exposure categories. Six children in the low group (relative risk = 2.0) and 7 children in the high group (relative risk = 2.1) had urinary system anomalies. In the low group, the defects included meatal stenosis (N = 3), ureteropelvic junction obstruction (N = 2), and lateral displacement of ureteral orifices (N = 1); in the high group, they included meatal stenosis (N = 3), ureteropelvic junction obstruction (N = 2), cystic kidney (N = 1), and ureteral diverticulum (N = 1). Again, the defects were varied and do not differ from the range of defects seen in the comparison group. Although the number of children with nervous system anomalies was too small to be analyzed, we noted an increasing rate with increasing paternal dioxin level. The 2 children in the low group and 2 of the 3 children in the high group had neural tube defects. In the 3 children in the comparison group, the birth defects were congenital hydrocephalus with cerebral atrophy, macrocephaly, and cerebral atrophy with microcephaly. The 3 children in the low category of other and unspecified anomalies had VATER association, hypoplastic adrenals secondary to anencephaly, and a liver hamartoma. Of the 16 risk ratios for contrasts of anomaly rates in the low- and high-dioxin categories with referent rates, 11 indicated increased risk, and 5 indicated decreased risk. Of the 8 contrasts of anomaly rates among children of Ranch Hands at background levels with those of comparison veterans, there were fewer indications of increased risk than decreased risk.

Of the 12 specific birth defects and 4 disabilities, only 2 disabilities (delays in development and hyperkinetic syndrome) provided sufficient outcomes for formal analysis. Counts and rates of those specific birth defects and disabilities too sparse to analyze are shown in Table 5.

Table 6 summarizes analysis results comparing major birth defects, specific delays in development, and hyperkinetic syndrome with paternal dioxin exposure.

TABLE 5. Numbers of Specific Anomalies and Developmental Disabilities by Paternal Dioxin Level*

Anomaly	Comparison	Ranch Hand		
		Background	Low	High
Anencephaly	0	0	1	0
Spina bifida	0	0	1	2
Hydrocephalus	1	0	0	0
Cleft palate	4	0	0	0
Cleft lip/palate	2	1	1	0
Esophageal atresia	0	0	1	0
Anorectal atresia	0	0	0	1
Polydactyly	0	0	0	1
Limb reduction deformities	3	0	1	0
Hypospadias	6	0	2	2
Congenital hip dislocation	9	2	2	1
Down syndrome	3	3	0	1
Disturbance of emotion	4	3	0	3
Mental retardation	3	2	1	1

* Denominators are liveborn infants (Table 1).

TABLE 6. Two Specific Anomalies and Two Developmental Disabilities by Paternal Dioxin Level

Outcome	Comparison	Ranch Hand		
		Background	Low	High
Major birth defects				
Number	56	17	23	19
RR*		1.1	1.7	1.2
95% CI		0.6–1.8	1.1–2.7	0.8–2.1
Multiple birth defects				
Number	4	0	3	1
Specific delays in development				
Number	71	24	26	21
RR		1.2	1.5	1.1
95% CI		0.8–1.8	1.0–2.3	0.7–1.7
Hyperkinetic syndrome				
Number	32	14	6	10
RR		1.5	0.8	1.1
95% CI		0.8–2.8	0.3–1.8	0.6–2.3

* Denominators for risk are liveborn infants (Table 1).

Counts and rates of multiple birth defects by dioxin category are also given but not analyzed, owing to small counts. There is an increased risk of major defects among children of Ranch Hands in the low (relative risk = 1.7) category, and a greater indication of increased risk than decreased risk in the low and high categories, and all of the elevated odds ratios are less than 2.0. The defects in the 8 children with multiple congenital anomalies were reviewed, and no consistent pattern was noted.

There were 4 children with recognized clinical syndromes known or suspected to be attributable to a single gene in etiology; all were fathered by comparison subjects: achondroplasia (N = 1), Treacher Collins syndrome (N = 1), Sturge-Weber syndrome (N = 1), and Albright syndrome (N = 1).

Discussion

Most investigations of the effects of dioxin on the reproductive system have focused on exposed female rodents and their offspring. Researchers have identified a range of teratogenic abnormalities in fetuses after the mothers were fed varying amounts of dioxin, but few researchers have examined the reproductive effects of the father's exposure to dioxin. Only a few studies have evaluated the mating behaviors and reproductive success of male rats after exposure to dioxin at levels causing systemic toxicity. Mating behavior, litter size, and birth defect rates were not affected by the father's exposure in one study,[14] but the mating index decreased, sterility increased, and the pregnancy index was normal in a second study.[15] Because of interspecies variation, the applicability of these animal studies to humans has been questioned.

All prior studies of the reproductive effects of dioxin in humans have relied on broad assumptions concerning the degree of dioxin exposure rather than upon direct measurement. Many studies have essentially been case reports, in which researchers made no attempt to verify actual dioxin exposure. In the birth defect studies conducted by the government of Australia[16] and by CDC,[12] researchers were unable to classify Vietnam veterans by their actual dioxin exposure but only evaluated differences between Vietnam and non-Vietnam veterans. In studies of miscarriages among residents of Alsea, OR, in 1978, researchers were unable to determine the actual dioxin exposure of individual women.[17] The lack of validated measures of dioxin exposure in these studies severely limits their interpretation.

Other studies were limited by small size as well as a lack of valid exposure assessment.[18,19] For example, in studies of birth defects subsequent to a 1976 industrial accident in Seveso, Italy, there was no apparent increased risk of major birth defects among the offspring of dioxin-exposed mothers, but the number of children of mothers with the highest likelihood of exposure was too small to assess specific categories of anomalies.[20]

Recently, investigators have concentrated on the direct effects of dioxin in cultures derived from fetal animal tissue.[21–24] They have identified dioxin effects in neural, palate, and kidney tissues. As in other animal studies, the applicability of these results to human paternal exposure remains debatable.

We found increased risk in some organ system categories, but the defects showed no pattern of differences across exposure categories and did not differ from the range of defects seen in the comparison group. We found an increased rate of nervous system anomalies in the Ranch Hand group, and 4 of the 5 Ranch Hand children with nervous system anomalies had neural tube defects, a pattern consistent with a previous study,[12] but sparse data precluded formal statistical analysis. These results provide no definitive evidence that paternal dioxin exposure causes birth defects or any of the other adverse reproductive outcomes that we studied. Our findings do not eliminate the possibility that particular subgroups of anomalies that we were unable to examine (owing to small numbers) might be associated with paternal dioxin exposure, but the overall pattern is generally not supportive of large or widely expressed adverse effects.

In spite of a fairly large population, the rarity of specific anomalies leads to many imprecise measures of association, as indicated by the wide confidence intervals that we report. For many anomalies, small numbers prevented us from strong inferences on the most heavily exposed Ranch Hands.

The serum dioxin results are accurate,[8] but they were assessed up to 26 years after exposure in Vietnam. Our initial dose calculation was based on a first order decay law.[25] The presumption of a constant dioxin half-life must be considered approximate in light of recent findings that the rate may depend on percentage of body fat.[26] At present, there are insufficient data from which to derive an alternative decay rate model based on body fat or changes in body fat.

Confounding by other maternal or paternal characteristics is another concern. Although we adjusted for maternal smoking and drinking during pregnancy, the

father's race, and parental ages, we were unable to adjust for paternal smoking and drinking, because we did not query the father regarding his habits at the time of each conception. Recently, paternal exposures to alcohol and tobacco were found to be positively associated with some anomalies and negatively associated with others.[27] Our studies, however, have found no important association between paternal smoking and dioxin[6] or between alcohol consumption and dioxin,[6] reducing the possibility of confounding.

It is unlikely that the results in this study are biased because of differential reporting, because the existence and content of birth certificates, newborn clinic records, or death certificates are not easily influenced by parents. In addition, these data were collected before the fathers knew their dioxin assay results. Nevertheless, we were concerned that Ranch Hand parents may have actively sought medical evaluation to detect possible birth defects in their children, making birth defects more verifiable in their children than among children of comparison veterans. We found no evidence of this "verification" bias.[9] We also investigated selection bias for the dioxin assay and found that children of enlisted nonflyers who volunteered for the dioxin assay, regardless of their exposure group, were more likely to have birth defects than were children of enlisted nonflyers who were not assayed. This "assay" bias is negligible because the effect does not vary with the father's exposure group.

Overall, these data provide little or no support for the theory that paternal exposure to dioxin is associated with adverse reproductive outcomes after service in Southeast Asia.

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VETERANS AND AGENT ORANGE - UPDATE 1996

STATEMENT
OF
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UNDER SECRETARY FOR HEALTH
DEPARTMENT OF VETERANS AFFAIRS
BEFORE THE
HOUSE COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

APRIL 16, 1996
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Mr. Chairman and Members of the Subcommittee, good morning.

I am pleased to be here to discuss the recently released Institute of Medicine (IOM) report, **Veterans and Agent Orange -- Update 1996**, and VA's initial response to the IOM findings. With me at the table are Dr. Susan H. Mather, Chief, Public Health and Environmental Hazards Officer; Mr. J. Gary Hickman, Director, Compensation and Pension Service; and Mr. Walt Hall, Assistant General Counsel.

As you know, this most recent IOM report was mandated by the Agent Orange Act of 1991 (Public Law 102-4), which directs VA to contract with the National Academy of Sciences (NAS) for periodic reports reviewing the scientific evidence concerning the association between exposure to herbicides used in Vietnam and diseases suspected to be associated with such exposure. Public Law 102-4 called for the NAS to conduct an initial review and then subsequent reviews at least every two years for a period of ten years from the date of the first report.

In July 1993, the IOM released its initial report in response to this mandate. In this first report, the IOM established four categories of association between herbicide exposure and health outcomes. The categories were: (1) sufficient evidence of an association, (2) limited or suggestive evidence of an association, (3) inadequate or insufficient evidence to determine whether an association exists, and (4) limited or suggestive evidence of no association. The present report continues to use this classification.

In addition to bringing the scientific evidence up to date, at VA's request, the IOM report released on March 14, 1996, also addressed several specific areas of concern. These include (1) the relationship between exposure to herbicides and the development of acute and subacute peripheral neuropathy; (2) the relationship between exposures to herbicides and the development of prostate, hepatobiliary, and nasopharyngeal cancers; and (3) the relationship between length of time since the first exposure and the possible risk of cancer development.

The most recent IOM report found that most health outcomes belonged in the same categories that they were placed in as a result of the 1993 evaluation. There were a few exceptions. Four of the five outcomes placed in the category of sufficient evidence of an association in 1993 remained there. These conditions were chloracne, soft-tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's Disease. There were no additions to this category. Porphyria cutanea tarda was dropped from this grouping to the category of limited or suggestive evidence of an association.

Other changes in this latter category of a limited or suggestive evidence of an association were the addition of: (1) acute and subacute peripheral neuropathy, and (2) spina bifida in the offspring of veterans.

The IOM also moved skin cancer from the category of limited or suggestive evidence of no association to the category of inadequate or insufficient evidence to determine whether an association exists.

As you know, upon receipt of the 1996 IOM report, Secretary Brown established a special task force, to review the new findings, along with other available information, and to make recommendations to him. I chair this group. The other task force members include my counterpart in the Veterans Benefit Administration, Under Secretary for Benefits R. J. Vogel; Mary Lou Keener, VA's General Counsel; Dr. Lynn Goldman, Assistant Administrator of the Office of Prevention, Pesticides, and Toxic Substances with the Environmental Protection Agency; Dr. Richard Jackson, Director of the National Center for Environmental Health, Centers for Disease Control and Prevention; and Dr. Frances M. Murphy, Director of VA's Environmental Agents Service. We are supported by a large working group of experts and policy makers in VA, the Centers for Disease Control and Prevention, and the National Institutes of Health.

So far, the task force and its working group have met twice. We have another meeting scheduled for April 23. We expect to complete our review and have written recommendations to the Secretary by the second week of May.

I understand that the focus of today's hearing is the health effects in children of veterans exposed to Agent Orange in Vietnam, so I will direct my further comments to this area.

This report by the IOM underscores an issue which I have discussed internally in the VA on several occasions in the past 18 months that I have been with the agency, and it has prompted me to speed up a previously envisioned timeline for action. Let me briefly expand on this.

As a medical specialist in toxicology and occupational health, and as a public health official for most of the past decade, I have repeatedly dealt with questions and concerns about untoward or adverse reproductive effects among persons exposed to industrial, agricultural and other work environments similar to what our active duty military personnel confront. However, essentially no research has been done about reproductive outcomes among military personnel and veterans. I have found that to be both surprising and of concern. With up to 20 percent of active

duty personnel now being female, my concerns are heightened, since maternal exposure to toxicants are more commonly associated with adverse pregnancy outcomes than paternal exposures. However, I would hasten to add that experience from male agricultural chemical workers has certainly demonstrated that untoward reproductive effects can occur in males as well as females. In any case, I do not believe that enough attention has been directed toward potential environmental reproductive hazards of military. To address this deficiency, we are looking into establishing a VA Environmental Hazards Research Center for Reproductive Outcomes.

This proposed center would be specifically dedicated to investigating reproductive outcomes among veterans and their offspring. A preliminary draft of a request for proposal (RFP) to site such a Center has been prepared and is now being revised. If all goes smoothly, we could have this RFP distributed by the end of this month and an award made to initiate it by July 1, 1996. We would be establishing this Center with existing resources, and we will assess its ongoing funding needs as we progress.

This Center will almost certainly need to be a collaborative effort, working with other federal or state agencies that collect birth outcome data, which have experience with relevant chemical exposures, and which can draw data from an ethnically and culturally diverse population.

We will be happy to keep the Committee apprised of our progress in this regard as we move forward.

I would also take this occasion to briefly mention a very relevant research project that VA is conducting. In response to Public Law 99-272 (Veterans Health Care Amendments of 1986), VA is conducting a "Study of Reproductive Health Outcomes Among Women Vietnam Veterans." The study is a retrospective cohort study comparing the reproductive health outcomes of about 5,000 women Vietnam veterans to those of an equal number of women veterans who did not serve in Vietnam. This study will add to our knowledge of the possible adverse reproductive outcomes among veterans, including birth defects among their children, as a result of their service in Vietnam.

The feasibility portion of the study (Phase I) was completed in March 1995 with good results. A total of 481 of the 500 women veterans who were selected for the feasibility study were located (96.2%); and 93% of the women contacted agreed to participate in the study, resulting in an overall response rate of over 85% of living veterans. (This is very good for studies of this type.) A total of 276 veterans reported having had relevant medical conditions (e.g., pregnancies, malignancies, birth defects among children) and 92.4% of these women veterans agreed to release their medical records. Obviously, the relationship between the conditions and military service cannot be established until the records have been reviewed and the data analyzed. The full study (Phase II) is expected to be completed within the next two years.

Before concluding, I should note that VA's General Counsel advises me that VA lacks the authority to provide benefits or services on the basis of adverse health effects in children

which are shown to result from their parents' service experience. Our task force is evaluating whether current scientific data warrants a change in the law.

Finally, let me conclude these remarks by underscoring the need for more research regarding the possible reproductive effects of military service. This is an area that has received too little attention in the past but should be a high priority in the future.

Thank you for the opportunity to be here today. I will be glad to respond to your questions at this time.

WRITTEN COMMITTEE QUESTIONS AND THEIR RESPONSES

DEPARTMENT OF VETERANS AFFAIRS

RESPONSES TO POST-HEARING QUESTIONS
FOR KENNETH W. KIZER, M.D. M.P.H.
UNDER SECRETARY FOR HEALTH

CONCERNING THE APRIL 16, 1996 HEARING
ON
THE EFFECTS OF HERBICIDES ON INDIVIDUALS EXPOSED
WHILE SERVING IN VIETNAM

FROM
HONORABLE LUIS V. GUTIERREZ
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
COMMITTEE ON VETERANS' AFFAIRS

Question 1: Dr. Kizer, in the initial Veterans and Agent Orange report, the committee found limited/suggestive evidence of an association for three cancers: respiratory cancer, prostate cancer, and multiple myeloma.

The 1996 update continues to support the classification of these diseases in the category of limited/suggestive evidence.

However, Vietnam veterans with prostate cancer have not received compensation. Why have other second-tier illnesses been compensated and not prostate cancer?

Answer: On May 28, 1996, President Clinton announced that VA would add prostate cancer to the list of diseases that are recognized as associated with exposure to certain herbicide agents for purposes of presumptive service connection. Although prostate cancer was included in category 2 in the National Academy of Sciences Institute of Medicine's schema in its 1996 update as well as the initial report, it is not VA policy to automatically recognize all such diseases. Rather, it is the Secretary's responsibility, under Public Law 102-4, to make determinations, based on reports received from the NAS (as well as other sources), as to whether there is sound medical and scientific evidence of a positive association between human exposure to an herbicide agent (i.e., a chemical in an herbicide used in support of U.S. and allied military operation in the Vietnam Conflict) and a disease. Secretary Brown established task forces in 1993 and 1996 to assist in analyzing the information in the NAS reports. The 1993 task force concluded that the credible scientific evidence in support of an association between exposure to herbicides and prostate cancer did not equal or outweigh the evidence of no association. However, the 1996 task force, that I chaired,

carefully examining all available data (including several studies not available to the 1993 task force) reached the conclusion that the credible evidence for an association between herbicide exposure and prostate cancer was equal to the evidence against such an association.

Question 2: Dr. Kizer, unlike studies conducted with regards to other illnesses, the three studies that led the NAS to find limited or suggestive evidence that an association existed between spina bifida and herbicides exposure were all conducted on veterans themselves rather than on groups outside the Vietnam veteran population.

I believe this is important. With regards to spina bifida, it means we do not have to extrapolate information from non-veteran groups and apply it to Vietnam veterans.

Will this fact influence the determination of the VA Task Force with regards to recommending compensation to the children of veterans with spina bifida?

Answer: The task force recommended that the "Secretary establish a presumption of service connection for spina bifida in the offspring of Vietnam veterans based on exposure to an herbicide agent if statutory authority is enacted granting such authority." Clearly, the task force members were impressed by the fact that the studies considered involved Vietnam veterans.

On July 25, 1996, Secretary Brown transmitted to Congress proposed legislation that would benefit eligible children through the provision of health care for disabilities associated with spina bifida, vocational training, and a monthly allowance in recognition of their special financial needs.

Question 3: Dr. Kizer, I assume that the VA Environmental Hazards Research Center for Reproductive Outcomes that you mentioned will include specific research into Agent Orange and its effects on reproductive health and birth defects. Is this correct?

Besides Agent Orange research, what other areas will this center focus its research on?

Answer: The initial thrust of a new VA Environmental Hazards Research Center for Reproductive Outcomes will be to conduct research related to the effects of herbicide exposure, such as Agent Orange, in Vietnam on reproductive health and birth defects. However, the intention of establishing this Research Center is to provide VA with the

capability to conduct research on the reproductive and developmental consequences of military service in general. Experience since WW II has shown us that the potential effects of military service on the ability of veterans to conceive healthy children is of great concern to veterans. Thus, although the initial emphasis will be on Agent Orange, this Center will be open to other areas of research on reproductive and developmental health.

NATIONAL ACADEMY OF SCIENCES
2101 CONSTITUTION AVENUE
WASHINGTON, D. C. 20418

INSTITUTE OF MEDICINE

August 16, 1996

The Honorable Tim Hutchinson
Chair, Subcommittee on Hospitals and Health Care
Committee on Veterans Affairs
U.S. House of Representatives
335 Cannon House Office Building
Washington, DC 20515

Dear Mr. Hutchinson:

This is in response to your July 31 letter, forwarding two questions from Mr. Gutierrez regarding the work of the Institute of Medicine (IOM) committees examining the health effects in Vietnam veterans of exposure to herbicides.

1. Dr. Tollerud, where do you believe the committee should focus its research for the next biannual update? ...Will any research be conducted in these areas in the next two years?

Under the Agent Orange Act of 1991 (codified as 38 USC Sec. 1116), the committees formed by the IOM are directed to "review and evaluate the available scientific evidence regarding associations between diseases and exposure to dioxin and other chemical compounds in herbicides" rather than conduct research on these associations themselves. For the next biannual update, the committee will continue to fulfill the congressional mandate to examine adverse health outcomes and "determine (to the extent that available data permitted meaningful determinations): (A) whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association; (B) the increased risk of the disease among those exposed to herbicides during service in the Republic of Vietnam during the Vietnam era; and (C) whether there exists a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease."

The committee shares your interest in research regarding women's health and reproductive difficulties and would be pleased if our efforts stimulated more work on these important issues. We are aware of research being conducted by the Department of Veterans Affairs on women veterans and of DVA's interest in fostering new research on reproductive problems. Any research published by DVA or others on women's health and reproductive difficulties will be addressed by the committee in the next update.

2. Dr. Tollerud, you mention on page 3 of your testimony that the Institute of Medicine will work with the Department of Veterans Affairs on a historical exposure reconstruction that follows up on the research in the 1994 report. Could you shed some light on this effort for the committee? In particular, what is the end goal of this project and when will its findings be released? In addition, will the Institute of Medicine be conducting any of its research in Vietnam? Has this option been considered?

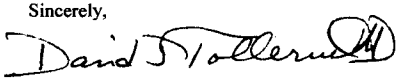
Under the sponsorship of the Department of Veterans Affairs, IOM has formed a committee to oversee the development and evaluation of models of herbicide exposure for use in studies of Vietnam veterans. This committee is presently writing a Request for Proposals (RFP) for such research. Present plans call for the RFP to be circulated later this year and for DVA to subsequently fund one or more research proposals generated in response to it. This research will not be conducted by the committee or the IOM.

The goal of this research is to develop models or other information that could be used to characterize the exposure of Vietnam veterans to Agent Orange and other herbicides. The committee has not yet formed an opinion on how long it might take to conduct the research fostered by the RFP.

The research proposals generated in response to the RFP will need to address the modeling of herbicide exposure of veterans; the means to accomplish this end will be at the discretion of the respondents. It is therefore possible that respondents could propose exposure assessment research that would be conducted in Vietnam, if it would inform the issue of veterans' exposure. The committee is aware of research previously conducted in Vietnam and heard presentations from scientists regarding this work at an exposure assessment workshop it held in May of this year.

Thank you for your continued interest in the work of the committee. Please feel free to contact me with any additional questions or concerns you or the Subcommittee may have.

Sincerely,



David Tollerud, MD, MPH
Chair, Committee to Review the
Health Effects in Vietnam Veterans
of Exposure to Herbicides

bcc.
David A. Butler
Karen Hein
Jim Jensen
Michael A. Stoto

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