CRITIQUE OF THE SECTION ON IMMUNE SYSTEM DISORDERS IN THE 1993 IOM REPORT "VETERANS AND AGENT ORANGE"

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As you know, on July 27, 1993, the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides reported on page 696 in "Veterans and Agent Orange" (hereafter referred to as the IOM report) that there was "inadequate or insufficient evidence to determine whether an association exists between exposure to herbicides and immune modulation or autoimmunity". After, critical review of the section on "Immune System Disorders" in the IOM report ("Veterans and Agent Orange"), we have come to the conclusion that this section of the IOM report was insufficient; in that, it inadequately reported on the statistically significant research data that shows the human immune system modulation associated with exposure to dioxin and other similar planar toxic chemicals, existing within the scientific and medical literature. Also, the section on "Immune System Disorders" of the IOM report seems to misinform its readers in many instances.

For example, on page 692, in the first paragraph, the IOM report states: there was "no observed increase in infectious or immune-mediated disease in the populations examined". "Immune-mediated disease" is defined by the IOM report authors on page 692 as "immune enhancement and autoimmunity" and "hypersensitivity disease" is defined as "autoimmunity"; so why does the autoimmunity, a statistically significant excess of positive ANA profiles [not mentioned by the IOM report, see page 698], documented by Jennings et al. (1988) not qualify as "immune-mediated" disease? In fact, the IOM report states, on page 698, that the findings from Jennings et al. (1988) "are compatible with, but not necessarily diagnostic of SLE [systemic lupus erythematosus] or a related connective tissue disease". Further, a positive ANA (anti-nuclear antibodies) profile by definition is a manifestation of autoimmunity. Autoimmunity by IOM definition is "immune-mediated disease". So why, didn't the IOM report mention, that the research data showing the existence of autoimmunity associated with dioxin exposure, was statistically significant (the positive ANA profiles in Jennings et al., 1988). (See epilogue for more on ANAs.)

Also, on page 698, the IOM report cites "an increase... ...of anti-nuclear antibodies (in one assay but not in another)...". However, according to Table 2, page 702, in Jennings et al., there were 8 vs. 0 ANA positive when Hep2 cells used (one assay) and 5 ANA positive subjects in the exposed group to none in the controls when the rat liver substrate was used (another). Thus, there was an increase in ANA profiles in both substrates; however, only one substrate produced significant results. Why did the IOM report minimize these findings?

On page 694, the first paragraph, the IOM report cited Stehr et al. (1986) and Webb et al. (1987) for finding "no effect on immune function". However, Stehr et al. (1986) found "a higher prevalence of palpable axillary lymph nodes in the low-risk group ($P < .05$) and a

trend suggestive of a greater prevalence of palpable nodes in the low-risk group" [p. 19]; and Table V., page 689 of Webb et al. (1987) shows a statistically significant result for the absolute T8 cell count. Why didn't the IOM authors mention these significant results? In addition, individuals chosen for study in both of these pilot studies were not chosen randomly; so selection bias was possible.

Also, on page 694, the IOM authors cite Webb et al. (1987), for having "T cell subset changes... ...in a different pattern" than Hoffman et al. (1986); Knutsen et al. (1987); Stehr-Green et al. (1987); & Andrews et al. (1986). This is a curious statement, because Hoffman/Knutsen et al. both have a control group and Webb et al. has only a comparison between high and low risk groups. Are these really comparable?

On page 694, the second paragraph, the IOM report authors cited Hoffman et al. (1986) but did not mention all the statistically significant results reported by the authors.

> "...statistically significant decreased percentages of T3, T4, and T11 cells..." [Hoffman et al. (1986), p. 2035]
> "...non-T peripheral lymphocytes... ...significantly greater..."
> "...an increased response to pokeweed mitogen (P<.05)."

On page 694, second paragraph, the IOM report cites Evans et al. (1988) as failing "to confirm (this) anergy" detected in Hoffman et al. (1986). However, Evans et al. (1988) only had a 56% participation rate and admitted on page 275 that "(t)hose returning for testing... ...were significantly younger than the nonparticipants, particularly those in the exposed group (24 vs. 37 yr)". Is Evans et al. valid?

On page 694, the last paragraph, the IOM report authors cite Webb et al. (1989) for "increased TCDD levels were correlated with increased numbers of T cells". However, Webb et al. (1989) did not have a control group; so no contrast can be made with the general population.

> "Six values were significant by multiple regression after controlling for age and sex: IgG, %T3, %T8, number of T8, %T11 and %T4; so were LEU 8 POS." [Webb et al. (1989), p. 187]

On page 694, last paragraph, the IOM report cited Webb et al. (1989) for "(n)o adverse clinical disease was associated with TCDD levels"; however, Webb et al. did report the following findings after physical examination of the study subjects: [p. 187]

> "...three persons presented with hirsuitism..."
> "(o)ne patient with hepatomegaly and peripheral neuropathy had a TCDD level of 430 ppt..."
> "...four persons had abnormal pain sensation..."
> "...five persons had abnormal vibratory sensation..."
> "...five had abnormal reflexes..."

On page 695, first paragraph, the IOM report cited Pocchiari et al. (1979) [not cited in the references, but believed to be Annals NYAS 320:311-320, 1979] for "(n)o abnormalities were found in many of the

immune parameters tested". However, Pocchiari et al. (1979) was "a progress report of the epidemiologic work" and as such "part of the relevant information pertaining to the health of residents in the contaminated area has not yet been adequately evaluated" [p. 319]. And close reading of the concluding sentence of the immunology section of Pocchiari et al. suggests that no statistical trend analyses were done comparing the data sets from the 4 immunologic screenings completed at that point in time: "(s)tatistical evaluation of the results obtained at any time tested did not show any significant immunologic difference between exposed and control children" [p. 316].

Also, the IOM authors did not mention that the immune parameters cited from Sirchia (1980) and Tognoni and Bonaccorsi (1982) were statistically significant results that were found in the other studies of the dioxin exposed children from Seveso. In fact, one of these cited study authors Sirchia, in 1982, wrote a report on the immune system of the exposed children of Seveso for the National Research Council (NRC). (Compare Sirchia below with Pocchiari above.)

Sirchia (1982), National Academy Press, reports that the children had six immunological screenings and in the exposed when compared with the controls, CH50 was significantly increased at all screenings. And Sirchia also reports that results from the first three screenings showed a significantly increased PHA and PWM and a trend toward elevated PBL during all screenings in the exposed vs. controls.

(From: VA, Review of the Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins, Vol. III, 1984, page IV-194,195.)

Why, wasn't this NRC document cited? So, where is the balance in the IOM report? Why weren't the statistically significant results from the immune function tests of the exposed Seveso children mentioned by the IOM report? For example, from JAMA 256:2687-2695, 1986:

> In Mocarelli on page 2694, we find, "Exposed children showed higher titers of total hemolytic complement activity in serum than controls in all the screenings; they also had lymphocyte responses to phytohemagglutinin and pokeweed mitogen significantly higher...".

On page 695, third paragraph, the IOM report cited Stellman et al. (1988) for producing a study based on "self-reported" information and suggested that this self-reported data was not reliable because it only "indirectly measured herbicide exposure". The IOM report is correct that the Stellman's Agent Orange Exposure Index used in their 1988 research report is based on self-reported information which is then compared with the HERBS tape data base of recorded USAF spray herbicide missions. However, the Stellmans state on page 318 (Stellman and Stellman, Am. J. Ind. Med. 9:305-321, 1986) "insofar as no veterans could possibly know the thousands of dates and places of missions on the tape, there can be very little selection bias in this measure. Even, were a veteran to know which locations were highly publicized `hot spots,' he would have to report his presence there at the right time to achieve a high score. In this study, one of our quality

control procedures entails editing of all subject-reported dates at specific Vietnam locations against his dates of Southeast Asia service and overall military service." "Therefore, we believe this to be an independent and objective source of exposure information... ...we infer that it would be quite difficult for a subject to deliberately fabricate a high score for himself." Thus, it seems that the IOM report may have mis-characterized the true nature and value of the Stellman's Exposure Index. (See epilogue for more about this index.)

Furthermore, this Exposure Index that was developed by Steve and Jeanne Stellman was used by the Federal court in MDL-381, the Agent Orange Product Liability Litigation, to determine which Vietnam Veterans were exposed and thus eligible for payment from the settlement fund. Thus, curiously, an Exposure Index approved by a senior Federal judge was found to be lacking by the IOM report.

Also, on page 695, the IOM report cites Stellman et al. (1988) as showing results consistent with "immune suppression". However, the Stellmans do not even use the word immune or even immune suppression in describing the significant results, from a symptom scale, that was associated with combat and herbicide exposure in Vietnam Veterans.

On page 695, the IOM report cites Kahn et al. (1992) but did not report any of the statistically significant results found because the IOM authors claim "the inconsistency of control values with expected laboratory control levels, and the lack of differences between the exposed and the nonexposed Vietnam veterans, reduced the relevance of these data to the present report". However, the results in Table 3, page 14 of Kahn et al. (1992), show that for T-RFC, Suppressor T8, and B(SmIg+) the statistically significant differences between Vietnam Veterans and control groups seem to be relevant because these results differ with nonexposed Vietnam Veterans controls.

Furthermore, on page 14, in Kahn et al. (1992) we find the following: "Excluding TCDD and TEQ there are 64 comparisons in Table 3, of which 4 would be expected to show significance at the .05 level by chance alone. However, 10 comparisons have p values < .05, and several other values approach significance. These differences are therefore not likely to be due to chance."

On page 695, last paragraph, the IOM report authors cited Eisen et al. (1991) for "(n)o significant effect on the immune system was observed". However, in Eisen et al. the word immune system is not used nor was the physical health of the veterans assessed for immune system problems. (See the list of health problems assessed on page 51 of Eisen et al.) Again it seems the IOM report authors are misleading the readers.

On page 696, of the IOM report, Newell (1984) is cited as showing "an increase in the percentage of cells in a subset of T cells"; however, on page 698 Newell is cited as reporting "a small decrease in the total number of T cells and an increase in the number of so-called active T cells". Again, the IOM report failed its readers, because both of these T cell subsets were found statistically to be significantly different in the Vietnam veteran group. For example, from Newell page 18, we find:

> "...the Active T-RFC was higher among the Vietnam veterans than among the matched controls, (P less than 0.05)."
>
> "This test measures the % of Active T-cells which is the subpopulation of T-lymphocytes that function as immune surveillance cells."
>
> "These cells are a subpopulation of the total T-RFC cells, which is reflected in a decrease of the % total T-RFC among Vietnam veterans compared to matched controls, P less than 0.05)."

ALSO, HOWEVER, THE IOM REPORT FAILED TO MENTION THAT KAHN ET AL. (1992) AND NEWELL (1984) FOUND THE SAME STATISTICALLY SIGNIFICANT TREND IN EXPOSED VIETNAM VETERANS FOR ACTIVE T-CELLS.

> On page 16, in Kahn et al. (1992), in the second sentence of the first paragraph under the heading "Comparisons of Lymphocytes Tests: Exposed vs Controls:", we find that "(r)osette forming T cell (T-RFC) results were interesting... ...a significant difference (p<.03), with the exposed being higher than Pooled Controls." On page 7 of Kahn, the last paragraph, a explanation indicates that the active T-RFC was being measured.

Why would the IOM report not discuss, or even mention for that matter, consistent results from two different studies done on Vietnam Veterans showing significant immune system modulation in the exposed group?

On page 696, third paragraph, the IOM report cites Wolfe et al. (1985, 1990) for the statement: "(s)tudies to date of individuals involved in Operation Ranch Hand... ...have not revealed any indication of overt immune suppression". However, on page 692, in the introductory paragraph for the section on "Immune System Disorders" the IOM report states that: "(f)ollowing a method recently outlined by the CDC [Centers for Disease Control] for categorizing effects on the immune system, immune suppression, immune enhancement (reviewed collectively here as immune modulation)...". Accordingly, the IOM report should be focusing on "immune modulation" not "immune suppression". It seems as though the IOM report authors did not follow the CDC guidelines when writing their report. Thus, the issue is immune modulation, not immune suppression or immune enhancement!

The statistically significant immune modulation data below is from the Lathrop et al., the 1984 AFHS Ranch Hand Report, the report Wolfe et al. 1985 used to write their article on the Ranch Hand Study.

> "No statistically significant group differences are noted except in Control #1 where the Ranch Hand group was found to have a lower unstimulated proliferation rate {Control #1 p=0.031}." [p. XVI-2-9]

The IOM report continues on page 696, third paragraph, by claiming that: "...most studies have indicated no effect on the immune parameters examined". The enclosed chart, updated in 1989, was included with our 1988 written testimony submitted to the

U.S. House Veterans Affairs Committee and subsequently published on page 286 in the permanent record of the hearing, Scientific Research on the Health of Vietnam Veterans, #100-51, held on June 8, 1988.

Furthermore, again on page 696, third paragraph, the IOM report authors claim that: "(t)he few parameters that were altered indicated an increase and are discussed further below". The issue is not if the immune parameter increases or decreases but whether the immune system is modulated!

On page 696, third paragraph, the IOM report cites the CDC [Vietnam Experience Study - VES] (1988) for "no effect on immune parameters in the cohorts studied". But, the IOM fails to mention, on page 135 of Monograph Volume III, the CDC (1988) states that: "(s)ince even before the study begun, we were concerned that possible exposure to dioxin and stress in Vietnam might suppress the immune system,...". However, the CDC claims "...we were reassured to find no evidence of... ...lymphocytopenia.. .". However, in Appendix D, Table D.2, page 275, CDC Monograph Volume III shows a statistically significant result for "(l)ymphocytes relative <16%" in the Vietnam Veteran cohort. [Please notice that data for "(r)ed blood cells <4.4 m/mm " is also significant.] And again, on page 189 of Volume III, the CDC claims that: "(t)he proportions in each cohort with values above or below the reference ranges for all test measurements were similar (see Appendix D)." Why does the CDC deliberately misinform their readers about these significant exam results? And why does the IOM report fail to mention these significant results from the CDC VES?

On page 696, fourth paragraph, the IOM report cites the 1982 AFHS [Air Force Health Study], Ranch Hand II Study (1984), as showing an "increase in the erythrocyte sedimentation rate [sed rate]". However, on page 4 of the 1987 AFHS published results we find this about the 1984 sed rate:

> "The sedimentation rate analysis revealed a highly significant group difference (p=0.002), due to a reversal of findings between examinations, i.e., a significant detriment in the younger Comparisons at the Baseline versus a significant detriment in the Ranch Hands at the followup."

Thus, there was no increased sed rate reported for Ranch Handers in the 1982 AFHS, rather the reported sed rate increase in 1982 was for the comparisons.

On page 697, fourth paragraph, the IOM report mentions "autoimmune thyroiditis" but then fails to cite Gaitan (1986). Eduardo Gaitan, M.D., Environmental Goitrogens Chief, Endocrinology Section, VAMC, Jackson, MS., states on page 273, in a chapter titled Environmental Goitrogens in the book "The Thyroid Gland" (1986) that:

> "For instance, an increased prevalence of primary hypothyroidism (11%) was documented among workers from a plant that manufactured PBB's and PBB oxides. These subjects had elevated titers of antithyroid microsomal antibodies, indicating that hypothyroidism

was probably a manifestation of lymphocytic autoimmune thyroiditis, perhaps a PBB-induced pathogenic autoimmune response..."

According to Dr. Gaitan, autoimmune thyroiditis was a manifestation of human exposure to PBBs, a planar molecule with similar toxic properties as dioxin. In fact, E.E. McConnell (NIEHS) states in an article, the Clinicopathologic Concepts of Dibenzo-p-dioxin Intoxication, (In: Banbury Report 18 - Biological Mechanisms of Dioxin Action, 1984, pp. 27-37) that:

"It is also apparent that the clinicopathologic syndrome induced by CDFs, PCBs, PBBs and CNs is comparable if not identical to TCDD." [TCDD = tetrachlorodibenzo-p-dioxin, CDDs = chlorinated dibenzodioxins., CDFs = chlorinated dibenzofurans, PCBs = polychlorinated biphenyls, PBBs = polybrominated biphenyls and CNs = chlorinated naphalenes]

"One can infer from this statement that the pathogenesis of the disease is the same, suggesting that these classes of chemicals involve the same cellular receptors."

"If one gives the most toxic isomer of each of the classes under discussion using the same experimental methods, the relative toxicity is CDD> CDF> PCB> CN." [p. 32]

The IOM report cited articles on the toxic effects of chemicals other than dioxin in the section on porphyria cutanea tarda (PCT); so, why did not the IOM report mention Dr. Gaitan's statement about autoimmune thyroiditis associated with PBBs.

Furthermore, on page 717 and 718, the IOM report cited Fitzgerald et al. (1989) and Lu et al. (1985) which both concern human exposure to PCBs/furans. Again, why didn't the IOM report on "Immune System Disorders" discuss research articles showing human immune modulation by toxic chemicals similar, in structure and toxicity, to dioxin?

The following studies showing human immune modulation by exposure to furans, PCBs, and PBBs were not mentioned in the IOM report: (not necessarily a complete list of all such studies not in the IOM report)

1. Kashimoto et al., 1979, Role of polychlorinated dibenzofurans in Yusho (PCB poisoning), Arch. Environ. Health 36:321.

2. Bekesi et al., 1979, Immunologic dysfunction among PBB-exposed Michigan diary farmers, Ann. N.Y. Acad. Sci. 320:717.

3. Chang et al., 1981, Immunologic evaluation of patients with polychlorinated biphenyl poisoning: Determination of lymphocyte subpopulations, Toxicol. Appl. Pharmacol. 61:58.

4. Chang et al., 1982, Immunologic evaluation of patients with polychlorinated biphenyl poisoning: Evaluation of delayed-type skin hypersensitivity response and its relation to clinical studies, J. Toxicol. Environ. Health 9:217.

5. Wu et al., 1984, Cell-mediated immunity in patients with polychorinated biphenyl poisoning, J. Formosan Med. Assoc. 83:419.

6. Elo et al., 1985, Recent PCB accidents in Finland, Environ. Health Perspect. 60:315.

7. Kochman et al., 1986, Phenotypical dissection of immunoregulatory t cell subsets in human after furan exposure, Chemosphere 15:1799-1804.

In addition, the following studies also not mentioned in the IOM report have each found an excess of autoimmunity associated with other xenobiotics; including pentachlorophenol, known to be contaminated with dioxins: (not necessarily a complete listing of all such studies)

1. McConnachie, Peter. R. and Zahalsky, Arthur C., 1991, Immunological consequences of exposure to pentachlorophenol, Arch. Environ. Health 46:249-253.

"Autoimmunity was evidenced by elevation of TA1 phenotype frequencies and a 21% incidence of anti-smooth muscle antibody [and anti-nuclear antibody]." [p. 249]

"Increased expression of CD26, associated with autoimmunity, is inferred from the finding of elevated Tal expression in progressive multiple sclerosis and increased Tal expression in conjunction with autoantibodies in cases of formaldehyde exposure." [p. 251-252]

2. McConnachie, Peter. R. and Zahalsky, Arthur C., 1992, Immune alterations in humans exposed to the termiticide technical chlordane, Arch. Environ. Health 47:295-301.

"There were tendencies toward... ...an increased frequency of CD26 in the T cell population...". [p. 298]

"Of 12 individuals tested for evidence of autoimmunity, 11 demonstrated some increased titer of a form of autoantibody." [p. 295] "...test results ranged from minor (anti-smooth-muscle titer 1:10) to severe (ANA, 1:640; anti-DNA, 1:80)." [p. 300]

"This cluster of significant findings demonstrates the emergence of aberrant peripheral T and B cell regulation and a potential for autoimmune activation, detectable up to 10 y after exposure to technical chlordane." [p. 295]

3. Thrasher et al., 1993, Immunologic abnormalities in humans exposed to chlorpyrifos: preliminary observations, Arch. Environ. Health 48:89-93.

"...two patients were diagnosed with either SLE or Lupus-like syndrome after their exposure." [p. 91]

"Increased expression of CD26 (TA1) cells, associated with autoimmunity, is inferred from observations on multiple sclerosis and following exposure to formaldehyde, chlordane/heptachlor, and PCP." [p. 92]

"Exposure to chlorpyrifos adds to and extends previous observations on xenobiotics."

"Therefore, the findings suggest that chlorpyrifos exposure is causally related to CD26 expression and autoimmunity." [p. 92]

Obviously, many studies showing human immune system modulation and autoimmunity associated with human toxic chemical exposure were not mentioned in the IOM report. Why?

On page 698, second paragraph, the IOM report cites Wolfe et al. (1990) by stating: "(e)arly results of the Ranch Hand study do not show any evidence of an increase in the signs and symptoms associated with connective tissue diseases"; but fails to mention the statistically significant excess abnormally high sed rates reported in the 1987 report. The IOM report did not inform its readers that increased sed rates are often found in individuals who have connective tissue diseases such as systemic lupus erythematosus (SLE); and, thus they did not inform the readers that recent results of the Ranch Hand Study did indeed show some evidence of an increase in the signs and symptoms associated with connective tissue disease. And, the IOM report fails to mention that the Ranch Hand Study did not actually examine study subjects for the presence of connective tissue or autoimmune diseases. Also, reported by the IOM on page 696, the 1987 Ranch Hand serum dioxin analysis, published in 1991, found statistically significantly excessive IgA in Ranch Handers and the USAF suggested that this was possibly evidence of a chronic inflammatory response. So, "early" results show "no evidence," but "later" results --showing evidence-- mentioned in another section were not cited again.

On page 698, in the second paragraph, the IOM report cited Wolfe (1990) for "changes in immune profiles of Ranch Hand veterans were also not observed". However, on page 67 of Wolfe (1990) we find that in "the composite skin test diagnosis, the unadjusted group contrast of the relative frequency of participants with possibly abnormal composite readings was significantly greater ($p=0.019$) for Ranch Hands than the Comparisons". And "without the cited interaction [lifetime cigarette smoking], a significant adjusted group difference ($p=0.011$) remained". Why did the IOM authors forget to mention the statistically significant skin test results reported by Wolfe (1990)?

On page 698, fifth paragraph, the IOM report cites the CDC (1988), Vietnam Experience Study [VES] (morbidity portion), as "fail[ing] to show evidence of connective tissue diseases"; however, the IOM report authors fail to mention that some autoimmune and/or connective tissue diseases, including SLE, were detected in the mortality portion of the VES published in 1987 [CDC, Postservice Mortality Among Vietnam Veterans, 1987, page 110]. Also, the IOM report fails to mention that the VES, nor any study for that matter, can not actually detect the

presence of all autoimmune connective tissue diseases because there is no specific ICD code for autoimmune diseases. Why does the IOM report mislead its readers concerning the detection of such diseases?

Again, on page 698, third paragraph, the IOM report cited Newell (1984) as showing "no medical problems associated with connective disease"; but do not explain that Newell did not specifically look for connective tissue disease. So, again the IOM statement is true, but very misleading.

On page 698, fourth paragraph, the IOM report cites the AFHS (1991) as failing "to show any difference in thyroid function between exposed and control veterans". However, on pages 15-102 - 15-104 in the AFHS (1991) we find the following:

> "Under both the minimal and maximal assumptions, the adjusted initial dioxin analyses found a significant negative relationship with T3 % uptake in its continuous form." [page 15-102]
>
> "Under the minimal assumption, the current dioxin-by-time interaction was not significant for all analyses, except for the adjusted analyses of T3 % uptake treated as a continuous variable (marginally significant results were noted for the unadjusted analysis of T3 % uptake and for the unadjusted and adjusted continuous analyses of FSH and fasting glucose." [page 15-103]
>
> "Under the maximal assumption, higher levels of FSH were associated significantly with dioxin among Ranch Hands with a later time since tour." [page 15-103]
>
> "Adjusted analyses also found that these Ranch Hands had significantly higher mean levels of TSH, fasting glucose, and 2-hour postprandial glucose than the background, and significantly lower mean levels of T3 % uptake and testosterone." [current dioxin level] [page 15-104]

The above results can be compared with statements from the 1984 AFHS report:

Lathrop et al., Air Force Health Study, Ranch Hand II: Baseline Morbidity Study Results, USAF School of Aerospace Medicine, Brooks Air Force Base, TX, Chapter XVI-6, 1984.

> "...decreasing T3 (triiodothyronine) uptakes are associated with advancing age in both groups with the slope being much steeper in the Ranch Hand group." [p. XVI-6-12]

The above 1991 AFHS results can be compared with statements from the 1987 AFHS report:

Lathrop et al., Air Force Health Study, Ranch Hand II: First Followup Examination Results, USAF School of Aerospace Medicine, Brooks Air Force Base, TX, October, 1987.

> "TSH (thyroid stimulating hormone) and testosterone means tests were statistically significant, and in the expected direction of a herbicide effect,...". [p. 33]

Also, the CDC VES found similar thyroid function test abnormalities:

Centers for Disease Control, 1988, Health Status of Vietnam Veterans, II. Physical Health, CDC Vietnam Experience Study, JAMA 2708-2714.

> "Vietnam veterans had about a 4% higher mean thyroid-stimulating hormone (TSH) level, a statistically significant difference."
>
> "Vietnam veterans were twice as likely to have a TSH value above 10mU/L." [A TSH value above 10mU/L = hypothyroidism.] [p. 2710]

Thus, it seems the IOM report is very misleading with respect to the AFHS (1991) thyroid function test results.

On page 699, fourth paragraph, the IOM report authors state in a summary paragraph of the section on "Immune System Disorders" that "at least a few positive results would be noted based on chance alone". However, the IOM report fails to mention that these so-called "chance" associations may be confirmed by a replication of the study in question. For example, the enclosed chart (see above) shows that many studies conducted by different researchers have found the same statistically significant results/trends in immune function in different cohorts with dioxin exposure. Additionally, as mentioned before, had the IOM authors accurately reported that Kahn et al. (1992) and Newell (1984) found the same statistically significant trend in exposed Vietnam Veterans for active T-cells; then again their claim of "chance" associations would not be consistent for some of the available data.

Incredibly, on page 694, the IOM authors cite Allison and Lewis (1986). Allison and Lewis (1986) is a letter to the editor of the JAMA by two employees of a chemical company responsible for dioxin contamination in Missouri. Why is this letter relevant? The IOM Committee was supposed to review epidemiologic studies not report on the opinion of Syntex Chemical Co.

On page 720 in the reference list, we noted that the IOM report only mentioned one state [Iowa - Wendt (1985)] survey of Vietnam Veterans. Why didn't the IOM report reference the many other available state surveys? A list of the other states with surveys follows: (not necessarily a complete listing) Illinois, Massachusetts, Michigan, Oklahoma, Oregon, Pennsylvania, Texas, Virginia, Washington, West Virginia and Wisconsin. Of course, one of the largest surveys of Vietnam Veterans is held by the Federal court in charge of MDL-381, the Agent Orange Product Liability Litigation and another is the Department of Veterans Affairs Agent Orange registry.

On page 692, first paragraph, the IOM report states: "(e)fforts are under way in animal studies to correlate such parameters with increased susceptibility to disease, but these analyses have not yet been

completed". However, the IOM report failed to mention animal study data (available for review) consistent with an association between exposure to dioxin and autoimmune and/or connective tissue disease. Again, this animal study data is presented below for further consideration. (Originally provided, by us, to the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides on September 9, 1992.)

1. Research focusing on prolactin in stalking the causes of lupus, The Norman (Okla.) Transcript, Friday, June 19, 1992, p. 8. (McMurray et al., J. Immunology, 1991; 147:3780-3787.)

   "Several small studies suggest excessive amounts of prolactin, a hormone made by the pituitary gland, may be partly responsible."

2. Jones et al., 1987, Circadian alterations in prolactin, corticosterone, and thyroid hormone levels and down-regulation of prolactin receptor activity by 2,3,7,8-tetrachlorodibenzodioxin, Toxicology and Applied Pharmacology 87:337-350.

   "The serum PRL [prolactin] concentration 7 days after TCDD administration was significantly higher ($p<0.05$) in TCDD-treated animals compared with that in pair-fed controls...". [abstract]

3. White et al., 1986, Modulation of serum complement levels following exposure to polychlorinated dibenzo-p-dioxins, Toxicology & Applied Pharmacology 84:209-219.

   "...(TCDD) suppressed serum total hemolytic complement activity (CH50)..."

   "Serum levels of complement component C3 were also suppressed..." [abstract]

   "...CH50 values..." "Following 14 days of recovery the lowest doses of HCDD (0.1 and 1.0 microgram/kg) had returned to control levels and were slightly elevated (131 and 119%) as compared to the vehicle control levels." [p. 213]

   "The complement activity of the HCDD low-dose groups continued to increase, with serum complement levels of 195 and 160% of the vehicle animals. With a 50 day recovery period, the low-dose HCDD animals were still significantly elevated (140% of control)...".

   "The high-dose HCDD animals, while not significantly different, had elevated CH50 levels which were 121% of the control group."

   "...the CH50 values... ...showed dose-related suppression and subsequent elevation...". [p. 214]

   "Our observation that exposure to PCDDs produces an elevation of the complement system is unique in that our mouse model reflects one of the most consistent immunological findings in humans

exposed to dioxins. Immunological evaluation of children exposed to PCDD-contaminated material released during the Seveso accident revealed a consistent elevation of complement levels over a 3-year period." (See Sirchia 1982 above.)

"The CH50 levels from all exposed children were significantly higher than unexposed age- and sex-matched control populations (Tognoni and Bonaccorsi, 1982; Sirchia, 1982)."

"As such evaluation of complement activity may represent a diagnostic tool in determining if PCDD exposure has occurred and a possible aid in determining the level of exposure."

Thus, "...properly conducted epidemiological studies might reveal a prevalence of autoimmune dysfunctions in high-risk groups exposed to dioxins." [p. 218]

The above statement is consistent with the following from McConnachie and Zahalsky (1991) [see A. above]:

"Evidence regarding immune dysfunctions and dysregulations following exposure to PCP and technical chlordane could extend to other polyhalogenated aromatic hydrocarbons and may have been the impetus for the induction of an autoimmune condition in some individuals."

Obviously, some animal studies which "correlate such [immune] parameters with increased susceptibility to disease" have been completed. Why were these studies not mentioned by the IOM report?

In summary, we believe that readers of this critique of the published results of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, titled "Vietnam Veterans and Agent Orange" (IOM report), will agree with us that the section on "Immune System Disorders" of this IOM report was insufficient, mainly because it failed to adequately report on all the statistically significant results found in the many human studies of immune modulation associated with exposure to dioxin and other similar and toxic chemicals.

Thus, not surprisingly, this IOM report, "Vietnam Veterans and Agent Orange", is consistent with past reports/studies from the VA, CDC, and USAF that also minimized and suppressed the effects of dioxin on the Vietnam Veteran populations studied. For example, Cate Jenkins reports on page 128 (Recent Scientific Evidence Developed After 1984 Supporting a Causal Relationship Between Dioxin and Human Health Effects, Affidavit for CV-89-03361 E.D.N.Y., Ivy et al. vs. Diamond Shamrock Chemicals et al., 1991) that a flawed Veterans' Affairs case control study of non-Hodgkin's lymphoma underestimated the risk for Vietnam Veterans. Also, the U.S. House Committee on Government Affairs found in a report titled "The Agent Orange Coverup: A case of flawed science and political manipulation," U.S. House Report 101-672 (1990), that certain high level executive branch government officials of the Reagan/Bush administrations deliberately caused the CDC Agent Orange Study of Vietnam Veterans to be canceled. And, Senator Tom Daschle

(The Congressional Record, Nov. 21, 1989, S-16540-46) found out that the USAF and the Reagan/Bush AOWG (Agent Orange Working Group) withheld or edited certain statistically significant associations from publication in the USAF Ranch Hand Studies.

We thought PL-102-4 mandated a report free from the distortions found in past USG (United States Government) funded Agent Orange Studies. We were wrong! No wonder Americans are losing faith in programs funded by their governmental institutions. Finally, since the IOM is actually not part of the USG, a formal scientific misconduct inquiry can not be made concerning what we believe was a deliberate attempt to misinform Vietnam Veterans, their families and the public at large about the potential dangers of dioxin on the human immune system.

Epilogue

A recently reported Vietnamese study also found a significant excess of anti-nuclear antibodies (ANA) in veterans exposed to Agent Orange/Dioxin.

According to Phan et al., Late effects of TCDD on cell-mediated immunity in Veterans who had lived in exposed areas of South Vietnam, In: Herbicides in War - The long-term effects on man and nature, 2nd International Symposium, Hanoi, Vietnam, 15-18 November 1993, Abstract Book, page 201-204.

> "In these 9 veterans, the anti-nuclear autoantibodies are detected in 3 with significantly higher titer of antibodies (1:1280)."
>
> "These obtained results give evidence (of) that there is an aceeleration [sic] of aging phenomena of the components of specific cell-mediated immunity in repeated dioxin-exposed veterans who had served in the South and Central areas of Vietnam in comparison with the control group. This aceeleration [sic] of aging phenomena is also expressed by the appearance of autoantibodies with higher titer in higher percentage of positive cases, while some non-specific arms of the immune system (such as NK cells and the IFN gamma) are higher in comparison with those of the control group." [p. 204]

Interestingly, the Vietnamese, Le et al., used the Stellman's Agent Orange index to show a:

Correlation between the exposure index of Agent Orange and Dioxin levels in adipose tissue in southern Vietnamese residents, In: Herbicides in War - The long-term effects on man and nature, 2nd International Symposium, Hanoi, Vietnam, 15-18 November 1993, Abstract Book, page 20-25.

> "The Agent Orange cumulative exposure index was calculated on the basis of two hypothesis (Stellman, 1986):" [p. 21]
>
> Reference... "3. S.D. Stellman & J.M. Stellman, Estimation of exposure to Agent Orange and other defoliants among American troops in Vietnam: a methodological approach." [p. 23]
>
> "The 22 subjects with a positive exposure index, the Spearman and Pearson correlation coefficients were 0.44 (p=0.04) and 0.5 (p=0.02) respectively (fig. 2) between dioxin levels and exposure index." [p. 22]
>
> "The correlation between dioxin level and exposure index determined in this study may assist future investigations into the health repercussions of Agent Orange." [p. 23]

This Vietnamese paper demonstrated that the Stellman Exposure Index is indeed a valid measure of self-reported exposure.