toxicology, the presence of a plausible dose-response relationship, and strength of association. But, meeting all of these criteria would not guarantee causality, nor would failing these criteria guarantee the lack of a dioxin effect. It can be argued, however, that the good faith application of these particular filters should be the starting point for generating hypotheses for experimental examination through in vitro and in vivo testing, as well as through further epidemiological analysis of these and other dioxin exposed groups.

**SUMMARY**

Based on the statistical findings of the 1992 examination, and subject to the qualifications considered above, the principal investigators have drawn the following conclusions.

**Glucose Intolerance**

The results indicate a statistically and potentially clinically significant association between serum dioxin and glucose intolerance. This association exhibits a dose response relationship, and is present both for non-diabetic individuals (as manifested by elevated insulin levels) and diabetic individuals (as manifested by increased prevalence and severity of diabetes, and decreased age of onset). This association was found with type II diabetes only. This association was also present longitudinally and occurs in other epidemiological studies in addition to the AFHS.

**Cardiovascular Mortality**

There is a statistically significant increase in cardiovascular mortality in the most heavily exposed subgroup, the enlisted groundcrew. This association persists longitudinally throughout the three examination cycles. Inclusion of this group with lesser exposed Ranch Hand subgroups results in a statistically nonsignificant overall relative risk. Less clinically severe criteria for altered cardiac functions including ECG findings of prior myocardial infarction, non-specific ST- and T-wave changes, and RBBB displayed significant positive associations with dioxin, although these associations did not cause significant group differences between all Ranch Hands and all Comparisons. Peripheral vascular function variables displayed significant subgroup differences for both the enlisted groundcrew and the high current dioxin category in relation to the Comparisons. Both groups had a greater prevalence of new pulse deficits arising since the 1985 followup examination than did their Comparisons.

**Serum Lipid Abnormality**

There is a highly significant positive statistical association between dioxin and cholesterol, dioxin and triglycerides, and dioxin and the cholesterol-HDL ratio in most models using either current dioxin levels or dioxin levels extrapolated to the end of the tour of duty in SEA. In such models, the correlation between HDL cholesterol and dioxin was highly significant and negative. These lipid findings were consistent with the 1987 findings, but were not consistent with the 1982 examination when serum cholesterol in Ranch Hands was significantly lower than in Comparisons.
Liver Enzymes

Both lipid-adjusted and whole-weight current dioxin showed elevated mean aspartate aminotransferase (AST), ALT, and GGT associations. For ALT and GGT this association was highly significant. This association had not been present in previous examinations. Although these elevations were statistically significant, mean enzyme levels remained well within normal limits and the prevalence of abnormally elevated liver enzymes was not statistically increased. Thus, although this laboratory finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Increase in IgA

A marginally significant increase in IgA with increased serum dioxin was found. This paralleled similar findings of increased IgA, first noted in the 1987 followup. Although this elevation was marginally significant, mean IgA levels remained well within normal limits, and the prevalence of significant abnormally elevated IgA was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Decrease in Serum Testosterone

A statistically significant inverse effect was seen between total serum testosterone and current dioxin in Ranch Hands. This paralleled similar findings first noted in the 1987 followup. Although this decrease was statistically significant, mean serum testosterone levels remained well within normal limits, and the prevalence of abnormally low serum testosterone was not statistically increased. Thus, although this finding is statistically significant, the AFHS population did not show any clinically adverse outcomes.

Decrease in MSK and Lupus Panel Positives

Significant and marginally significant decreases in the prevalence of positive reactions to MSK, lupus, and rheumatoid factor tests in relation to dioxin were seen in the 1992 followup. When present, these tests are indicative of potential autoimmune disorders. Their absence is therefore not normally considered pathologic, but a decreased prevalence could nonetheless indicate some degree of immune suppression. More specific tests of immune suppression were not significantly associated with dioxin.

No Significant Difference in Incidence or Prevalence of Neoplastic Disease

It has been theorized that dioxin can act as either an inducer or promoter of neoplastic disease. A detailed analysis of all forms of neoplastic disease over the course of a decade show no significant group differences in the incidence of benign or malignant neoplasms, including those neoplasms most often associated with herbicide exposure in the Ranch Hand population (e.g., Hodgkin’s Disease, non-Hodgkin’s lymphoma, soft tissue sarcoma). In the 1992 followup, there was again no significant group differences. The marginally significant differences in site-specific incidence that were found more often favored a decrease in relative risk associated with dioxin exposure rather than an increased risk. As previously
stated, because of its size, this study does lack power to ascertain modest increases in relative risk for uncommon neoplasms. As the population continues to age, the combination of an increase in background rate of neoplastic disease, increased time for latent effects of past exposure, and increased time of total exposure may combine to increase the power of this study to determine neoplastic effects.

In summary, glucose intolerance, serum lipid abnormality, and cardiovascular abnormality and mortality, are areas demonstrating associations that, if causality were established, would represent the most important dioxin-associated health problems seen in the AFHS to date. These three areas appear to have the greatest magnitude of effect in terms of absolute increase in risk, in common areas known to contribute to years of potential life lost and to overall healthcare costs. Clearly, there are biological interrelationships among all three of these variables that will make the task of establishing causality, as well as establishing primary versus secondary causality, challenging. From a public health perspective, these three areas demand the greatest attention.
A careful review of the results of the past four physical examinations provides an opportunity to refine and focus the remaining two examinations of the Air Force Health Study. The current and prior examination outcomes have identified several medical tests requiring more intense evaluation and other analyses that can be reduced or eliminated in the 1997 and 2002 studies without sacrificing scientific value.

Immunological testing of skin test reactivity, T-cell type, and T-cell function were important parts of all four examinations, and high-quality data in this area were gathered in the 1985, 1987, and 1992 studies. After exhaustive evaluation, there appear to be some effects that may be dioxin-related. Therefore, many of these measurements will remain in the 1997 study. However, the skin test reactivity measurement is medically redundant with the battery of cell function tests, and thus will be eliminated from the next examination. Additionally, many of the highly nonspecific tests in the protein profile and lupus panel will be eliminated. Many of these tests are poorly understood by clinical pathologists and immunologists and should be removed from consideration.

The Doppler evaluation of the large artery pulses (radial and femoral) also will be eliminated, reducing examination time and stress on the participants. Our data does not indicate any dioxin-mediated effect on these arteries. However, the relationship between dioxin and diabetes makes it imperative that the smaller arteries of the legs and feet remain a key part of the examination.

Because no association was found between testicular abnormality detected during ultrasound and dioxin, the ultrasound evaluation of the testicles will be eliminated.

Additional dioxin assays will be performed on willing Ranch Hands who have participated in our studies of dioxin half-life. A fourth measurement, taken from blood collected in 1997, will further refine our estimate of half-life, allow study of the fit of the first order elimination model, and permit better estimates of the initial dose in Ranch Hands with elevated current dioxin levels.

The 1997 examination will be expanded to include additional measurements of the cellular metabolism of glucose. The possible development of a laboratory measurement of specific enzymes involved in glucose transport into the cell would be an important addition to the current evaluation of diabetes.